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OBSERVATIONS ON THE TREATMENT OF LIPOID NEPHROSIS *

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THE disease known as chronic nephrosis or lipoid nephrosis has been the subject of continued dispute since the initial publications of Munk and of Epstein. Opinion still seems to be divided as to whether it is a type of glomerulonephritis or a distinct clinical and pathological entity. There is apparently an increasing amount of opinion favoring the latter view.

In a series of 14 patients, who have been carefully followed since their dismissal from the hospital, all are alive and consider themselves well. All of the 14 show at the present time a normal blood chemistry and are entirely free from edema or any other physical abnormality. Seven of them, however, still have an intermittent albuminuria. These patients have been under observation for periods varying from 10 to two years. What the future course may be would, perhaps, be hazardous to predict. At the present time, however, there is no evidence that would lead one to expect a recurrence of the old disease. The purpose of this communication is to report observations made on these patients with various types of therapy.

In a previous communication it has been pointed out that these patients apparently have an inability to store protein.[3] The observations of several observers, notably those of Collip,[2] indicate that Antuitrin "G" facilitates storage of nitrogen. Because of this fact it was thought desirable to try this method of treatment on a small series of patients.

Figure 1 shows the result of this treatment in one patient, a man, aged 30, who had symptoms of this condition for four months before this observation was begun. The patient received Antuitrin "G" in doses varying from 2 to 4 c.c. daily. No marked response occurred until one month after the injections were begun. At this time there was a marked increase in the total protein, an increase in the serum albumin and serum globulin, and a fall in the blood cholesterol.

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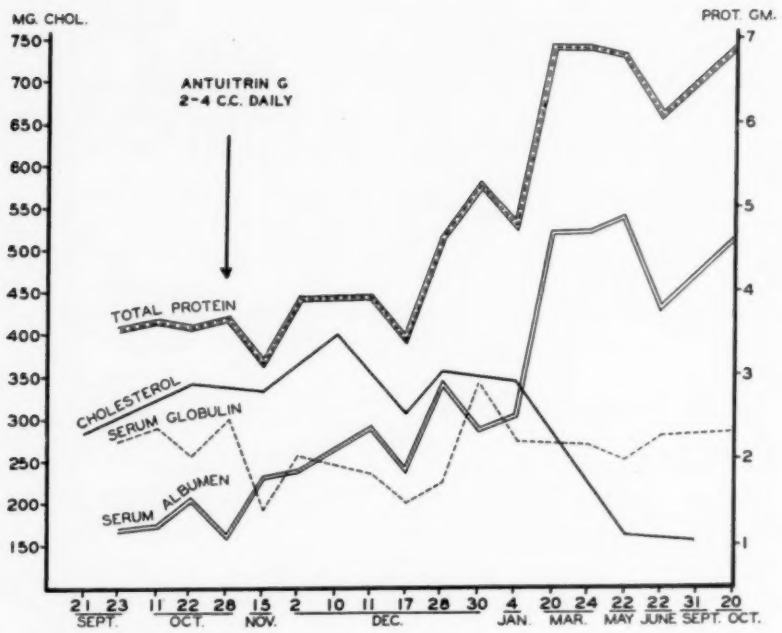

FIG. 1. The effect of the administration of Antuitrin G on the serum proteins and cholesterol in a case of lipoid nephrosis.

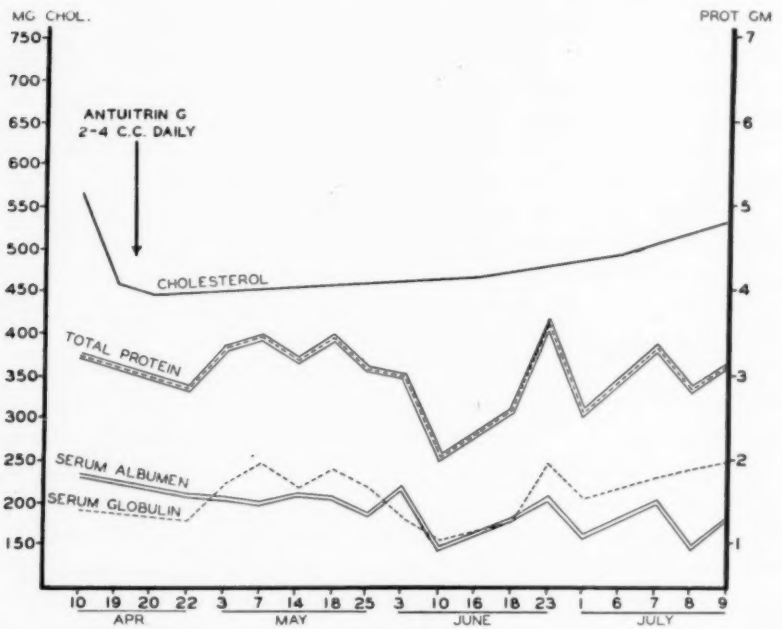

FIG. 2. The effect of the administration of Antuitrin G on the serum proteins and cholesterol in a case of lipoid nephrosis.

Encouraged by this result, the same method of treatment was followed in the second patient, a young woman, aged 20, who had been suffering from lipoid nephrosis for two months before this treatment was begun. No marked change in the blood chemistry was noted (figure 2).

The third patient, a man, aged 22, received the same treatment. Again no essential change was noted except the fall in the cholesterol which did not, however, fall to normal value.

Our impression from these observations and two others in which no improvement was noted, was that Antuitrin "G," at least in the doses employed, did not modify the course of the patient's illness. The apparently good result obtained in the first patient was probably due to the beginning of a remission of the disease, since he recovered very rapidly from this point on.

The high blood cholesterol shown by patients with lipoid nephrosis is one of the striking phenomena of the disease. In our experience, as long as the blood cholesterol is high the patient is liable to have a recurrence of edema, low blood protein and marked albuminuria. There is a strong suspicion in the minds of many that the underlying process in this disease is a disturbance in cholesterol metabolism. Until, however, the normal cholesterol metabolism is better understood we cannot hope to have a very clear idea of disorders of cholesterol metabolism. In our two fatal cases of lipoid nephrosis there were extensive deposits of cholesterol in the organs, especially in the liver and kidneys.

Best and Huntsman [1] have shown that the addition of choline to a diet high in fat prevents the deposition of fat in the rats' liver. This observation led us to study the effects of choline on patients with lipoid nephrosis. Five patients in all were studied and all showed similar effects. The observations on two of these patients are shown in figures 3 and 4. In both of these patients the administration of three grams of choline was followed by a preliminary marked rise in blood cholesterol and then a gradual fall. In one of these patients there was a coincident striking increase in the blood protein (figure 3), while in the other the increase was slight (figure 4). In the other three patients there were definite, but no striking increases in the blood protein, such as is shown in figure 3. A preliminary rise of cholesterol after ingestion of choline occurred in all five patients.

Adrenal cortex hormone was administered to four patients without our observing any striking or definite changes. Its administration was suggested by the observations of Thaddea and Fasshauer [4] who found that the administration of this hormone prevented hypercholesterinemia in adrenalectomized animals.

We have continued to obtain the best results, as reported previously, from the employment of a very high carbohydrate diet, varying from 600 to 800 grams of carbohydrate per day. We have also restricted the patient's intake of meat and made the diet as largely vegetable as possible, and in this way reduce the intake of cholesterol containing foods. Eggs are not allowed. We have also added large amounts of soy bean to the

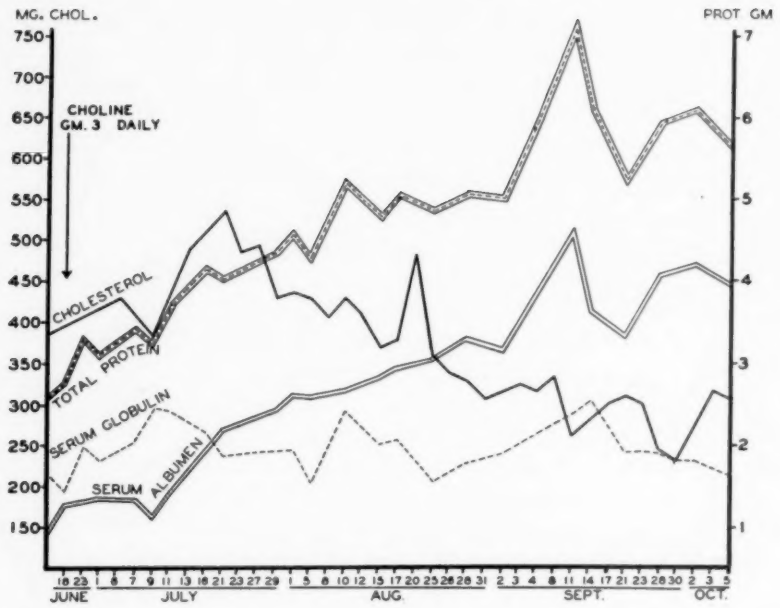

FIG. 3. The effect of the administration of choline on the serum proteins and cholesterol in a case of lipoid nephrosis.

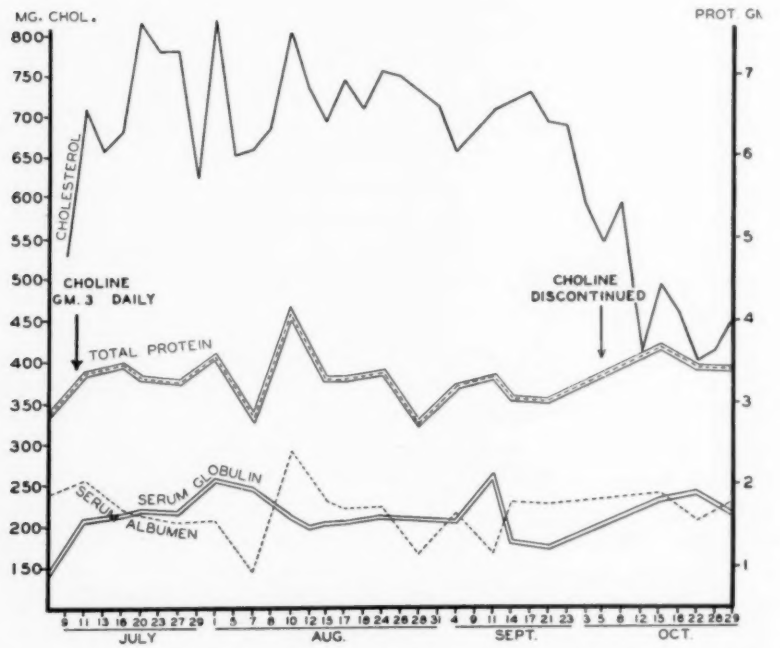

FIG. 4. The effect of the administration of choline on the serum proteins and cholesterol in a case of lipoid nephrosis.

diet, but have seen no specific effect upon the regeneration of blood protein. The results obtained in patients on a diet rich in soy beans have not, however, been striking.

Summary

The administration of Antuitrin "G," choline and adrenal cortex hormone have had no appreciable effect upon the course of lipoid nephrosis. In certain patients the ingestion of choline was followed by a fall in the blood cholesterol values. The best therapeutic results, thus far, have been obtained by employing a high carbohydrate diet combined with blood transfusions and diuretics.

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THE RENAL THRESHOLD FOR GLUCOSE; CLINICAL OBSERVATIONS ON A CASE OF NON-DIABETIC (RENAL) GLYCOSURIA *

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THE present day conception of the functional activity of the renal unit has changed the views of the clinician in regard to renal threshold for glucose. It is now believed that the glucose content of glomerular fluid approximates that of the plasma of arterial blood and that in a normal kidney under ordinary conditions, practically all of the glucose is reabsorbed in the first portion of the tubule. The so-called renal threshold is measured in terms of the level of blood sugar at which sugar appears in the urine. Actually, it depends entirely on the functional ability, at any given time, of the tubule to absorb all the sugar from the urine up to the "threshold" percentage amount.

We are presenting in this paper observations on a case of renal glycosuria that throw light on factors which influence the reabsorption of glucose.

CASE REPORT

R. R., a 39-year-old housewife, was admitted to the medical service of the Johns Hopkins Hospital on March 4, 1937, complaining of sugar in the urine and tumor of the womb. No one in her family had ever had diabetes or any other form of glycosuria. One brother had a small goiter that had never required surgical treatment The patient was born in North Carolina and had always lived in that state doing the housework on a small farm. At the age of about 12 years, she first became aware of a small goiter which grew gradually in size but never caused any symptoms. When she was 22, her only child was born and thereafter her health was poor. She nursed the child for a year and during that time sugar was found in her urine. After the child was weaned, the glycosuria disappeared. Thyroidectomy was performed and a goiter was in part removed, which, we infer from available history, was colloid and non-toxic in nature. When she was 24, her urine was examined and no mention of sugar was made. Thereafter for five years she felt very well but at the age of 29 the goiter began to reappear and with it she thought there was increased nervousness When she was 34 she had a severe respiratory infection, but her local physician made no comment after examining her urine. The following year, which was four years ago, when she was 35 years old, she was examined by another physician who reported finding sugar in her urine. She was hospitalized for tonsillectomy and told that her blood sugar was normal. After this the urinary sugar did not increase and it was thought that a low carbohydrate diet had no effect on its amount. She was allowed, therefore, to eat as she pleased. By preference she drank over a quart of milk a day, but otherwise her diet, except that she ate no potatoes, was that of the average Southern woman. She noticed no weight loss, undue sweating or tremor, heat intolerance, or increase in appetite. At no time had there been polydipsia, polyuria, or

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pruritus. Menorrhagia of two years' duration finally led to a diagnosis of myomata uteri and she came to the Johns Hopkins Hospital. Here because of the glycosuria, she was admitted to the medical service.

On admission temperature was 99.0°. Pulse: 86. Respirations: 22. Physical examination showed a rather thin but moderately well-nourished woman who did not appear ill. She was not nervous or overactive, and the eyes gave no evidence of exophthalmos or the associated eye-signs of hyperthyroidism. There was no tremor or undue sweating. No evidence of weight loss or dehydration was made out. There was an old thyroidectomy scar, beneath which in the mid-line lay a nearly spherical nodule about 4 cm. across. Most of this felt as if it were cystic. Throat, lungs and heart were quite normal. The liver edge could be felt just below the costal margin, and in the lower abdomen there was an irregular, firm mass which on pelvic examination proved to be a myomatous uterus. Extremities were normal.

On laboratory examination: Hemoglobin: 82 per cent (12.4 gm.). RBC 3,800,000. WBC: 6,350 with a normal differential. Sedimentation rate: 19 mm. in 1 hour. The urine was acid with a specific gravity of 1.045 and contained 5 per cent sugar (Benedict's quantitative method) all of which fermented with yeast. Three plus acetone was present but no diacetic acid. Albumin and casts were not found in the urine. The blood sugar was 80 mg. per cent (Folin-Wu 1929 method) and the CO_2 combining power was 54.1 vols. per cent. The reducing agent in the urine was shown by Dr. Mary Buell to be entirely made up of glucose; it was completely fermented by ordinary yeast, the osazone formed was a typical glucosazone and the Seliwanoff reaction excluded fructose. The blood Wassermann was negative. Further blood chemical studies included calcium 10.3 mg. per cent; phosphorus 3.9 mg. per cent; non-protein nitrogen 25 mg. per cent; urea nitrogen 12 mg. per cent; total proteins (Kjeldahl method) 6.39 gm. per liter; albumin globulin ratio 63/37; cholesterol on March 8, 492 mg. per cent; on March 17, 469 mg. per cent; and on April 29, 326 mg. per cent; and Van den Bergh, faint indirect trace. Basal metabolic rates varied from plus 19 to plus 6 without iodine treatment. The bromsulphalein test of liver function with 5 mg. per kilo resulted in no retention at the end of 30 minutes. The urine was sterile on culture. The urea clearance test gave a 65 per cent normal standard clearance. Phenolsulphonephthalein test on ordinary fluid intake was 54 per cent in two hours but during a period of forcing fluids to four liters a day was in the neighborhood of 100 per cent.

The diagnoses made were renal glycosuria; recurrent, nodular, non-toxic goiter; and myomata uteri. On March 22, a hysteromyomectomy with appendectomy was performed by Dr. C. S. Stevenson, and on April 17 a cystic adenoma of the thyroid was removed by Dr. P. Kunkel. The second operation was performed purely for cosmetic reasons and the tissue removed was cystic and did not contain any functioning thyroid elements. A postoperative B.M.R. was minus 1 per cent. The patient's rather brief stay in the hospital gave an opportunity for limited metabolic studies.

Observations: The patient was placed on a calculated diet with controlled fluid intake and four daily urinary collections, but no therapeutic insulin was given. Repeated blood sugars taken at various times of the day and night were always within normal limits. (See figure 1.) In spite of this, the patient showed a constant glycosuria that varied between 1 per cent and 10 per cent. It is interesting that the urine was never sugar free.

Acetonuria, which was present on admission, disappeared after 24 hours of adequate fluid and carbohydrate intake. It recurred for a short period after each of the operations and following the hysteromyomectomy was accompanied for over a day by a four plus test for dicetic acid.* The CO_2 combining power, however, never fell

*The excretion of large amounts of acetone bodies which was observed following both operations, has been noted as a characteristic of renal glycosuria cases by several authors. (Lewis and Mosenthal,[1] Allan and Vanzant.[2])

below 43.8 vols. per cent and as the patient again became able to take food and fluids, the ketonuria promptly cleared.† The initial high level of blood cholesterol (492 mg. per cent) fell to 326 mg. per cent after 7½ weeks of high carbohydrate intake.

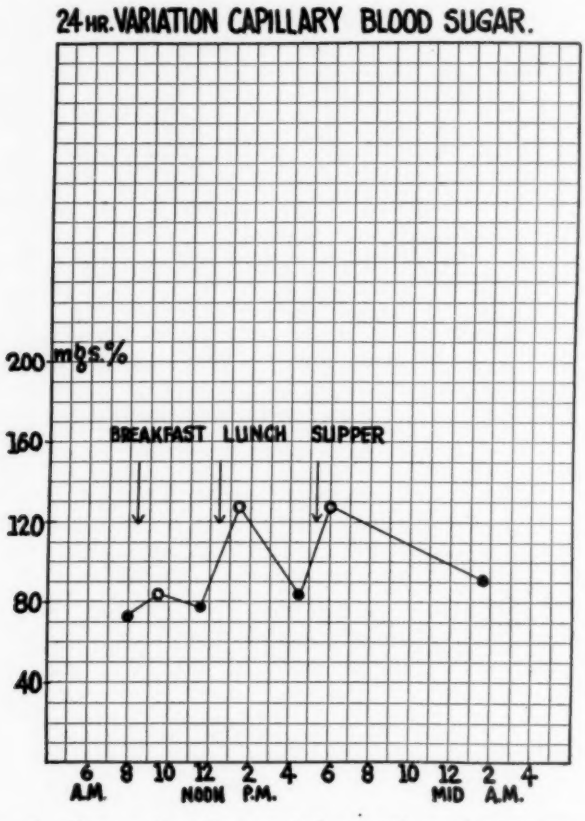

FIG. 1. Twenty-four hour variation capillary blood sugar.

A series of three glucose tolerance tests with simultaneous determinations of the respiratory quotients was performed by Dr. Edward M. Bridge (figure 2). On the initial test the respiratory quotient started at the low fasting value of 0.76 and rose to 0.86. The peak of the blood sugar curve was 218 mg. per cent in capillary blood (Hagedorn-Jensen method) but the venous blood sugar was not determined. A second test 12 days later started at 0.80 and rose to 0.93, and the third, performed after the patient had been in the hospital 38 days, gave high normal values with a rise of respiratory quotient from 0.85 to 0.97, a peak of capillary blood sugar of 197 mg. per cent and a venous blood sugar peak of 156 mg. per cent. Dr. Bridge pointed out that the patient was in a condition of partial starvation at the time of admission owing to the combination of a slight reduction of carbohydrate of the diet and the loss of glucose in the urine. On a high carbohydrate diet (350 gm.) the respiratory quotient curve rose to a high normal. During the third test simultaneous arterial and venous blood sugar (Hagedorn-Jensen method) curves (figure 3) revealed an entirely normal arterio-venous difference[4] (maximum of 41 mg. per cent) and the blood phosphate

† Joslin[3] says, ". . . ketosis develops during starvation rather than following dietary excesses. . . ."

level dropped from 4.3 to 3.5 mg. per cent, indicating active withdrawal of glucose during the passage of blood through the body tissues.

Two insulin tolerance tests were done by giving the patient two units of regular insulin intravenously. On each occasion there was a prompt fall in the blood sugar

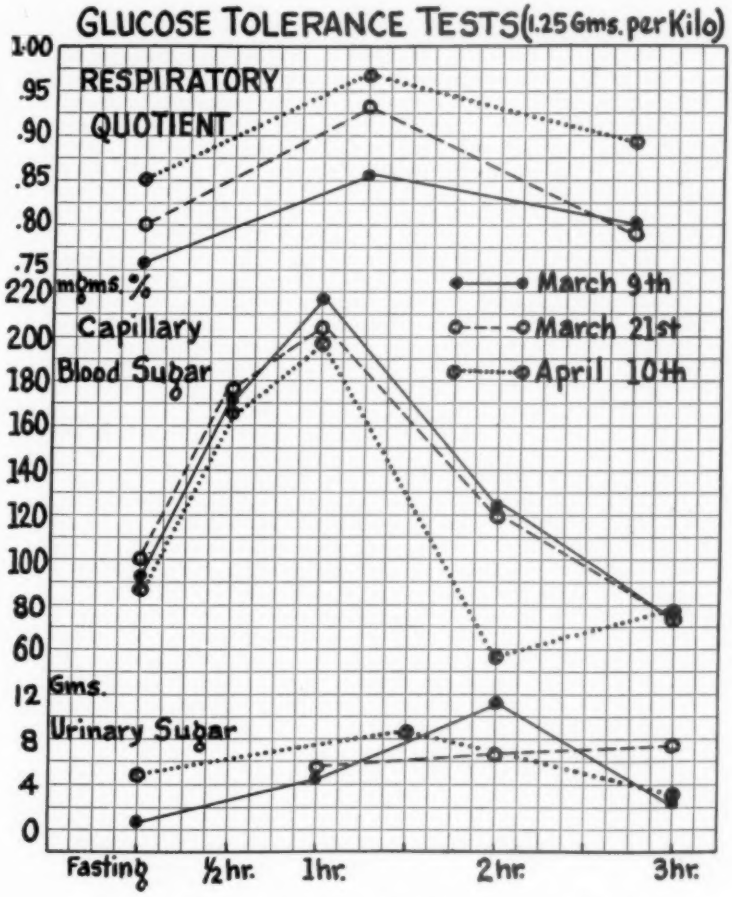

FIG. 2. Glucose tolerance tests (1.25 gm. per kilo.).

level (24 to 25 mg. per cent), indicating a normal sensitivity to insulin (figure 4). Moreover, although the blood sugar fell to 56 and 57 mg. per cent, the sugar did not entirely disappear from any one of the 15 minute specimens of urine. Intravenous insulin, three units before breakfast, and two units before the other two meals, had no apparent effect on the amount of sugar excreted in the urine in one 24 hour period. Three units of insulin intravenously produced marked hypoglycemic symptoms, but unfortunately no urinary or blood determinations were made while these symptoms were present.

On two occasions the patient was given 1 c.c. of pituitrin intramuscularly, while the fluid intake was carefully controlled. The second time the test was performed, while the patient was in a fasting state, there was definite decrease in the urinary output (table 1), but no comparable change in glycosuria. This agrees with obser-

vations by Poulsson [5] and by Burgess, Harvey, and Marshall [6] on the antidiuretic effect of pituitary extract during creatinine and xylose clearance tests. Moreover, the constant glycosuria indicates that neither the glomerular filtrate nor the tubular function of reabsorbing glucose is influenced in man by therapeutic doses of pituitrin.

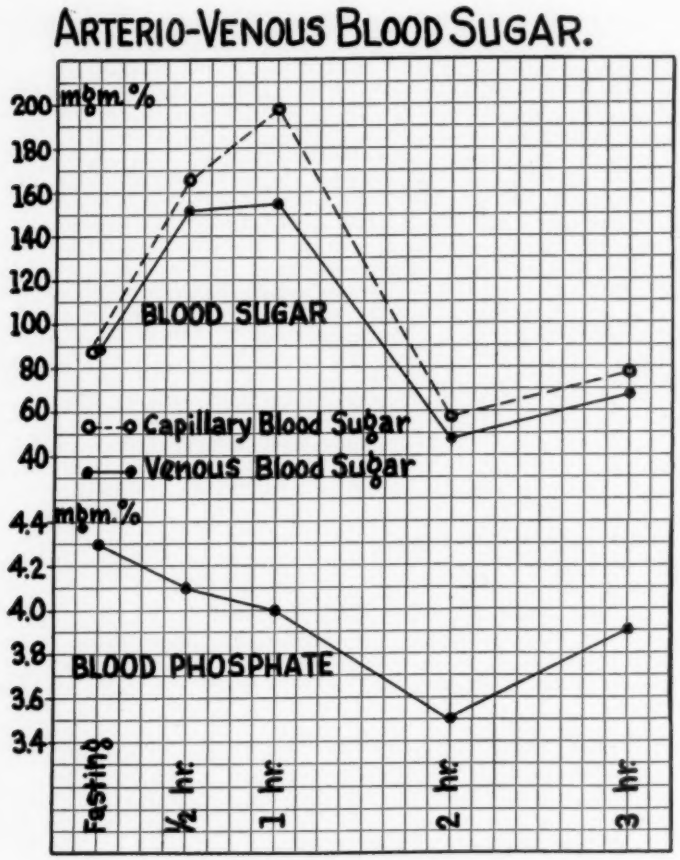

FIG. 3. Arterio-venous blood sugar.

TABLE I

Effect of Pituitrin on Renal Excretion of Sugar

Time	Fluid Intake	Urine in c.c.	Sugar in gm.	Sugar %
8:00 a.m.	250 c.c.	Specimen discarded		
8:30 a.m.		40	0.42	1.05
9:00 a.m.		100	0.45	0.45
9:02 a.m.	Pituitrin 1 c.c. intra-muscularly			
9:30 a.m.	250 c.c.	25	0.36	1.45
10:00 a.m.		13	0.39	3.00
10:30 a.m.		15	0.38	2.50

On April 16, simultaneous urea, xylose, and glucose clearances were performed.* The results were within the accepted normal variation for urea and xylose and are set forth in table 5. In the two test periods the urea and xylose clearances varied proportionately, the urea clearance being 62.6 per cent of the xylose clearance in period 1, and 60.5 per cent in period 2. The apparent glucose clearance was 40 per cent of the

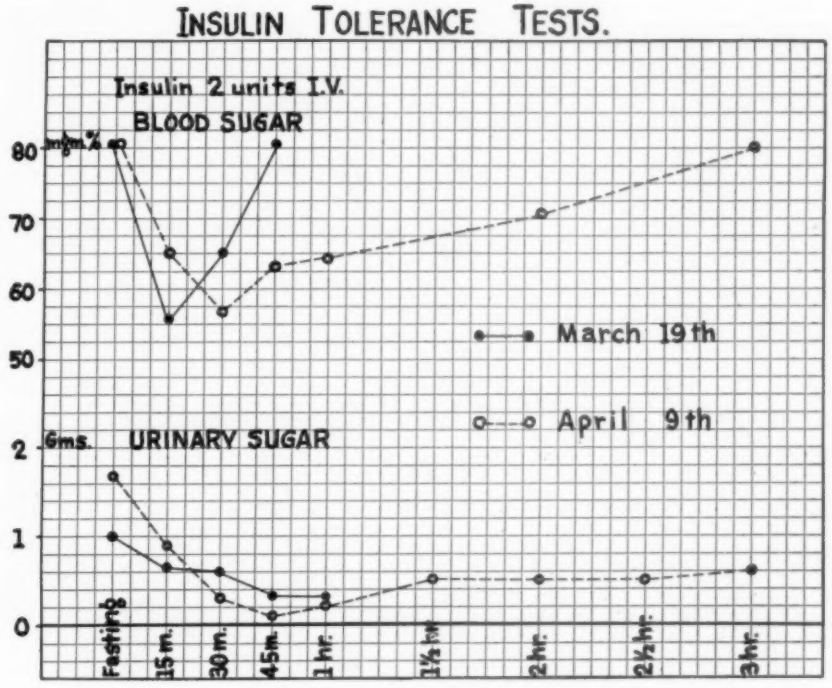

FIG. 4. Insulin tolerance tests.

xylose clearance in period 1 and 49 per cent in period 2. Although no further observations are available and none was made on arterial blood it seems probable that this difference is greater than could be accounted for by experimental error and is, therefore, real. This probability is given credence because of other considerations which will be pointed out in the discussion of the change in daily glucose excretion as affected by water excretion. The work of Homer Smith [7] and his collaborators indicates that inulin clearance is an accurate index of glomerular filtration and that xylose clearance gives figures amounting to about 75 per cent of the inulin amounts and is quite uniform. Recognizing, therefore, that xylose clearance gives results that are too small for the actual filtration figures, we can, however, use the xylose clearance as an index and calculate the amount of fluid and glucose filtered and reabsorbed. The figures are set forth in tables 2, 3 and 4.

We appreciate the fact that no sweeping conclusions can be drawn from these few tests. However, it is worthy of note that the two periods showed a distinct variation in amount of reabsorbed glucose per minute as well as in the percentage of

* These chemical determinations were performed by Mrs. Margaret White, in the Chemical Laboratories of the Johns Hopkins Hospital. The other chemical determinations reported in this article also were made in these laboratories, except those made by Dr. Bridge, in the Chemical Laboratory of the Harriet Lane Home.

glucose in the reabsorbed fluid. The similarity of the amount of filtered glucose per minute in the two periods is almost surely a coincidence. Why more c.c. of blood should be cleared of glucose when the blood sugar level was 58 mg. per cent than when it was 71 mg. per cent remains to be explained.

TABLE II

Xylose and Glucose Clearances

	Urine vol. in c.c.	Blood				Urine			
		Reducing substance mg. p. c.	After fermentation	Xylose after correction	Glucose after correction	Reducing substance mg. p. c.	After fermentation	Xylose after correction	Glucose after correction
Period I	84	200	112	151	71	7400	5300	7080	1310
Period II	96	162	90	121	58	6400	4400	5880	1350

TABLE III

Comparison of Urinary Concentration of Glucose and Xylose

	Urine vol. in c.c. in 1 hr.	Glucose			True Xylose			c. glucose / c. xylose
		in plasma mg. p. c. (Gp)	in urine mg. p. c. (Gu)	Concentration (C)	in plasma mg. p. c.	in urine mg. p. c.	Concentration	
Period I	84	71.3	1310	18.3	151	7080	46.8	0.40
Period II	96	58	1350	23	121	5880	48.6	0.47

TABLE IV

Estimated* Amount of Glucose That Is Reabsorbed

	Filtered fluid c.c. per min. (F)	Reabsorbed fluid c.c. per min. (R)	Filtered glucose mg. per min. (Fg)	Reabsorbed glucose mg. per min. (Rg)	Glucose mg. p. c. in reabsorbed fluid (Rg %)
Period I	65.5	64.1	46.6	28.3	44.2
Period II	77.7	76.1	45.8	24.2	31.8

$$F = C\ (\text{Xylose}) \times \frac{U}{60} \qquad R = F - U \qquad Fg = F \times Gp\ \% \qquad Rg = Fg - \frac{U \times Gu}{100}$$

* These calculations are based on the xylose clearance figures which have been shown by Homer Smith and his collaborators to be about 75 per cent of the inulin clearance which is thought to be an accurate index of glomerular filtration.

TABLE V

Comparison of Simultaneous Urea, Xylose, and Glucose Clearances*

	Urea clearance c.c. of blood	Xylose clearance c.c. of blood	Glucose clearance c.c. of blood	Urea clearance / Xylose clearance	Glucose clearance / Xylose clearance
Period I	41.3	66.2	25.8	62.6%	40%
Period II	47.2	78.0	38.2	60.5%	49%

* The difference between the blood sugar in venous and arterial blood probably should be taken into account but at low values is thought to be negligible.

On two occasions forcing fluids, the diet remaining constant, greatly augmented the glycosuria while restricting the fluid intake diminished it. Thus from March 14 through 16, with a daily intake of 1,050 c.c. the 24 hour outputs of urinary sugar were 25, 43 and 30 gm., while on the succeeding two days with intakes of 3,900 and 3,800 c.c., 80 and 112 gm. of sugar were lost. Again from April 1 through 4, on an average fluid intake of 3,990 c.c., the average daily glycosuria was 73 gm., while from April 5

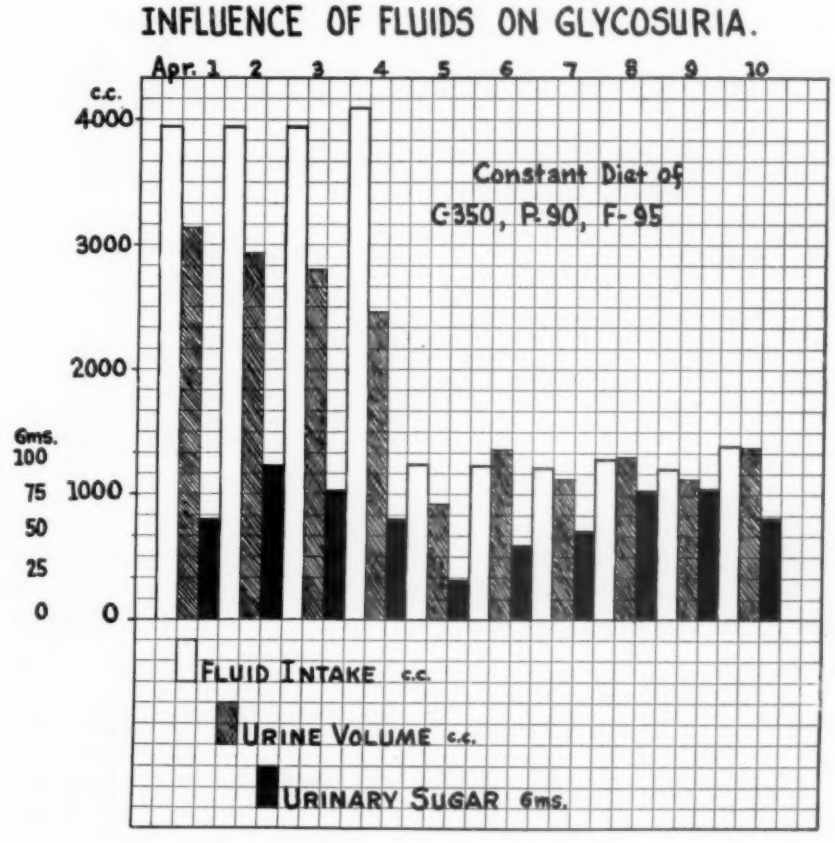

FIG. 5. Influence of fluids on glycosuria.

through April 10, with an average intake of 1,260 c.c., only 56 gm. on the average were spilled daily (figure 5). These changes were simultaneous with the sudden alteration in urinary output, but it is interesting that sustained reduction in the 24 hour urinary output failed to maintain a reduction in 24 hour sugar output. Thus from the second to the fourth day of forced fluids the sugar output declined progressively while after

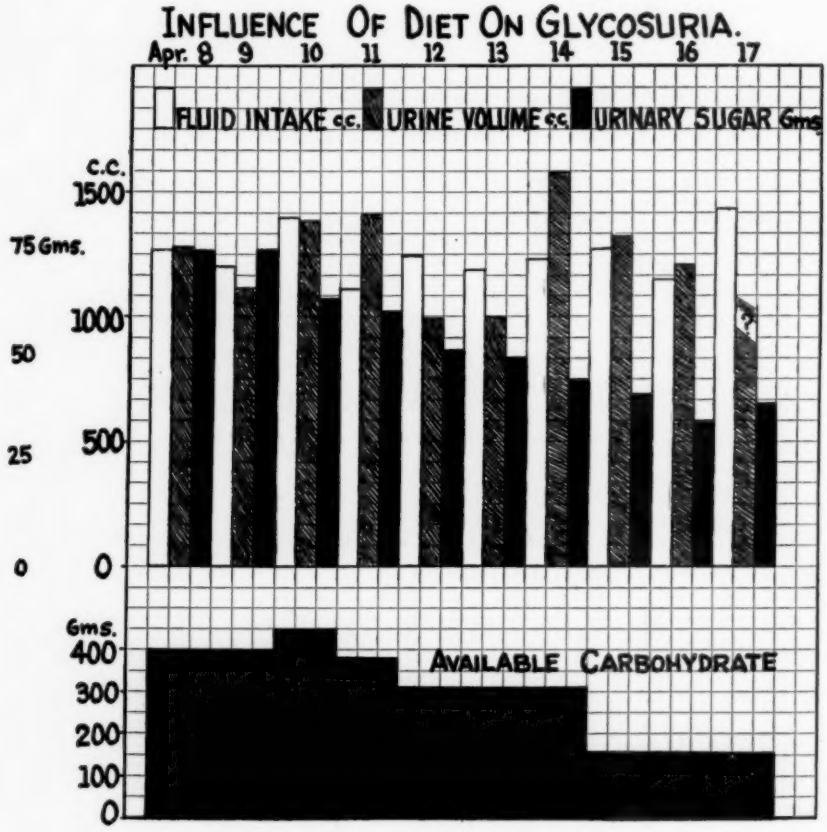

FIG. 6. Influence of diet on glycosuria.

the fluid intake had been sharply curtailed the output of sugar fell abruptly and then rose steadily to the average level. This secondary adjustment was of sufficient magnitude to obliterate entirely the initial effect so that on the third and fourth days of forced intake about the same amount or even a little less sugar was excreted than on the fourth and fifth days of restricted intake. With fluids restricted and the urinary output remaining fairly constant, this secondary adjustment obviously was expressed in a change in percentage of urinary sugar which gradually rose to a figure (10 per cent) which permitted the same amount of sugar to appear in the urine as when fluids were not restricted.

An attempt was made to alter the glycosuria by changing the carbohydrate intake while maintaining the fluid intake constant at 1,200 c.c. a day (figure 6). From April 5 through 10 on a diet of COH 350, P 90, and F 95 (402 grams of available COH by formula of Palmer and Ladd [8]) the average sugar loss was 57 grams.

From April 12 through 14 on a diet of COH 275, P 80, F 125 (321 gm. of available COH) the average loss was 48 gm. And from April 15 through 17, when the diet was COH 110, P 90, F 195 (162 gm. of available COH) the daily glycosuria averaged only 40 gm. These figures indicate that the carbohydrate intake had a slight but definite influence on the glycosuria.[1, 9]

The effect of a salt-free diet was also tried (figure 7). After a six day control period with salt as desired, the patient's diet, for four days, was made nearly salt-free, but without changing its food content or the fluid intake. A slight diuresis resulted

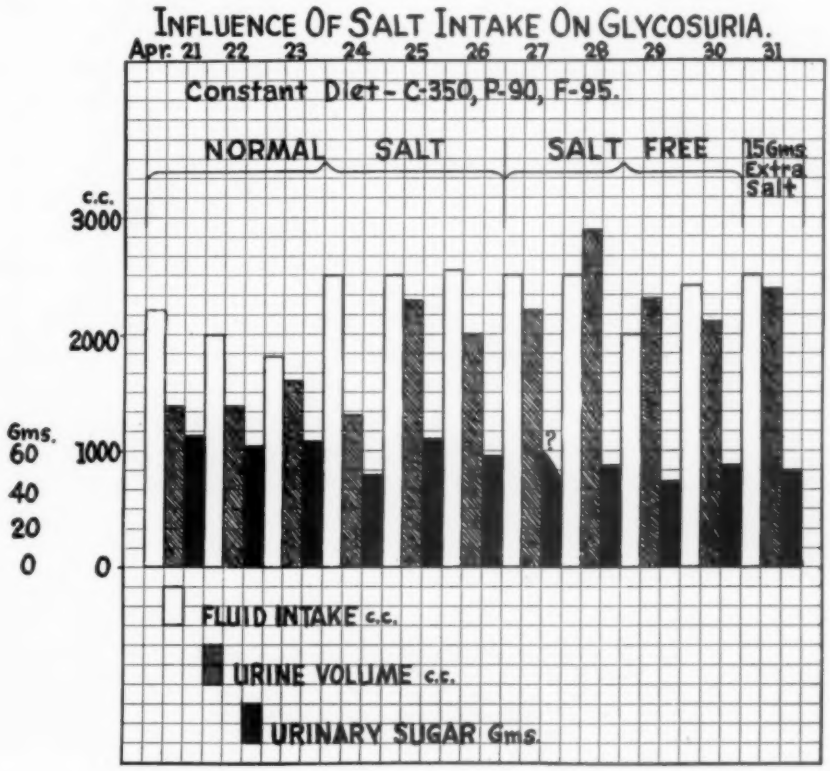

FIG. 7. Influence of salt intake on glycosuria.

which raised the average urinary output from 1,660 to 2,360 c.c., but in spite of this, the average glycosuria fell from 60 to 48 gm. This slight change seems hardly enough to indicate a reduction in the glomerular filtrate or an increase in tubular absorption of sugar during the process of conserving the bodily salt but it points to another factor which must be controlled in experiments on glucose-water balance. Studies of the effect of ingesting excess salt were cut short by the patient's return home, but, on one day of ordinary diet augmented by 15 gm. of salt, the sugar in the urine was unchanged (50 gm.). In short experiments Roch, Martin and Scicolounoff [10] noted a reduction in glycosuria when hypertonic salt solution was added to the slowly injected glucose solution but our experiments extending over days instead of hours are not comparable to theirs.

Comment

This case conforms to the criteria of true renal glycosuria. (*a*) The reducing substance in the urine was glucose. (*b*) The glucose tolerance curve was normal and at no time during the 24 hours did the blood sugar rise above 156, although Joslin puts the normal post-prandial limit at 170 mg. per cent. (*c*) The respiratory quotient revealed a normal utilization of glucose in the body, as did the fall in blood phosphate during a glucose tolerance test. (*d*) The patient gave no history of symptoms suggesting diabetes mellitus.

Many of the old criteria for the diagnosis of renal glycosuria can now be ignored.[9] In the first place whether or not glycosuria is constant depends purely on whether the blood sugar falls below the renal threshold at some time in the day. Since this depends on the height of blood sugar in relation to the threshold point and indicates a quantitative rather than qualitative difference, it seems useless to make such an arbitrary rule. In the second place, the carbohydrate intake does influence every case to a certain extent. This is graphically demonstrated in our patient by an increase in urinary sugar during glucose tolerance tests and a decrease after intravenous insulin (figures 2 and 4). Moreover, in patients whose carbohydrate metabolism is quite normal, as it was in ours, the amount of carbohydrate in the diet has little effect on the usual 24 hour blood sugar curve. It will be noted that in our case there was a definite but slight reduction in the amount of sugar excreted when the available carbohydrate in the diet was reduced from 402 gm. to 162 gm. (figure 6). This probably depends on a post-prandial variation in blood sugar level which constitutes a definite but small percentage of the 24 hour period of sugar excretion. In the third place, whether or not the individual subsequently develops diabetes mellitus [11] seems to us to have little to do with the diagnosis of non-diabetic glycosuria at any given time. Further facts are necessary before we comprehend the part played in the bodily economy of carbohydrates by the renal threshold.

Discussion

In a group of 25 healthy male medical students, Campbell, Osgood and Haskins [12] found "The renal threshold for true sugar varies from 99 to 228 mg. per hundred cubic centimeters, 80 per cent of cases having values that range from 140 to 190 mg." The subjects of their investigation ingested 500 c.c. of 50 per cent glucose, voided every five minutes and when the urine became positive for sugar, blood was drawn from the vein. Since the appearance time of glucose in the urine varies after intravenous injection from three to eight minutes (Robinson, Derivaux and Hewell [13]), and since they report that it took five minutes to determine a positive test and draw blood, and since the subjects voided only every five minutes, there was an experimental lag of 8 to 18 minutes. The blood sugar curve was rising during their observations and therefore even these values are somewhat too high.

In the light of these facts, it is not surprising that one occasionally encounters innocent glycosuria in individuals whose low renal threshold is surpassed by their blood sugar level.

In our case, the renal threshold was not accurately determined since 15 minute specimens of urine contained sugar even after the blood sugar had fallen to 56 mg. per cent. Since the observations of Hamman and Hirschman [14] in 1917, it has been thought that the renal threshold for sugar is lower once the secretion of sugar has begun. We believe that this difference in the appearance threshold from the disappearance threshold is more apparent than real and depends largely on the lag in observation time. However, Robinson, Derivaux and Hewell (1935) and Roch, Martin, and Sciclounoff (1936) believe that their observations confirm it. The threshold in our patient, therefore, might have been definitely higher than 56 mg. per cent if we had been able to lower the blood sugar to a point where no more sugar appeared in the urine and then to determine in the usual manner the threshold point at which sugar first made its appearance during the rise in blood sugar. We make this comment merely to point out the fact that the threshold in our patient is not to be compared with that of individuals in whom it is determined from a starting point of a urine which is free of sugar. In this connection, it is equally important to remember that arterial blood sugar values are the ones to be used in determining renal threshold since the blood in the glomerular capillaries is arterial. The difference between capillary whole blood sugar and arterial plasma sugar values is too negligible to warrant consideration (Olmsted [15]). At the fasting blood sugar level there is little difference between arterial and venous sugars, so that in cases with low thresholds these figures are much the same. As the blood sugars rise, however, the difference is increasingly great (figure 3) and in cases with higher thresholds this becomes an important factor which must be considered.

There has been much speculation as to whether or not the threshold changes in a given individual. Knud Faber [16] has paid much attention to the subject of renal threshold for glucose and he states that "the glycosuric threshold in diabetics just as in non-diabetics, has a constant value in one and the same individual, whereas in different individuals it may vary somewhat." However, Faber recognized the significance of the frequent occurrence in pregnancy of glycosuria with normal blood sugar. He studied two women during and after pregnancy. His method was to determine in the course of a glucose tolerance test, the point at which sugar appeared in the urine and then observe the height of the blood sugar. A week later, he administered a smaller dose of glucose and determined the highest blood sugar level obtainable without any glycosuria. This method allowed him to place the threshold below one point and above another. By these means he showed that the threshold rose some months after parturition from below 132 to above 197 in one case and from below 132 to above 150 mg. in the other. Williams and Wills [17] publish a great many glucose

tolerance tests on pregnant women in the early and later parts of pregnancy and following delivery. From these they conclude that ". . . the lowering of the renal threshold, though a factor in all the glycosuric cases, is not the major one in its causation of the glycosuria of pregnancy, but rather it is the association of the lowered threshold with an abnormally raised blood-sugar curve. Only 4 out of 21 cases of glycosuria were simple renal leaks . . .".

It may not profit us to speculate as to the nature of the change in renal threshold which accompanies the temporary endocrine and hormonal imbalance during pregnancy.[19] It does seem cogent, however, to point out the fact that since the renal threshold for glucose depends on the function of the kidney tubules, there may be some association with the disturbance in water balance often encountered in pregnancy in which the kidney tubules, and the effect of posterior pituitary extract on them,[6] play a part. The pituitary alteration which occurs during pregnancy may account for the pregnancy drop in renal threshold.*

We have no complete explanation for what occurs when there is an abrupt change in the water balance. When the daily fluid intake was increased from 1 liter to 4 liters, the sugar in the urine rose from 30 to 112 gm. In our second experimental period, however, we noted that on a constant fluid intake (4,000 c.c.) and a constant diet (available carbohydrate 402 gm.), the urinary sugar, having first risen, fell on successive days from 92 gm. to 76 gm. to 61 gm. Conversely when the fluid intake was suddenly restricted to 1,200 c.c. a day, the urinary sugar fell to 25 gm. and then rose to 46 gm. to 52 gm. to 77 gm. To know just how the tubules were functioning on each of these days, we would first have to know how much glomerular fluid and glucose were being filtered. This might be learned by frequent glucose and xylose or inulin clearance tests.[7] Then if the glucose clearance varied differently from the inulin clearance, one could infer a change in tubular glucose absorption or, in other words, a temporary change in renal threshold. Without this information we cannot fully comprehend the change in excretion of sugar caused by large changes in fluid intake. Some of the variable factors are (*a*) the height of the blood sugar, (*b*) the amount of glomerular filtrate, (*c*) the amount of water reabsorbed by the tubules, and (*d*) the amount of sugar reabsorbed by the tubules.

On an absolutely constant diet and constant exercise regime, one would expect the blood sugar in a normal individual to behave in a constant manner even under the conditions of sudden change in water balance. In our patient the amount of glucose lost in the urine might tend, if anything, to lower the blood sugar level during the period of forced fluids.

* In discussing our observations and deductions with Dr. Gerty T. Cori [18] she showed one of us charts setting forth results obtained in experiments she had just performed on normal and hypophysectomized rats. These experiments were devised to elucidate the effect of epinephrine on muscle glycogen, blood sugar and glucose tolerance in normal and hypophysectomized rats. To our great interest the hypophysectomized rats developed higher blood sugars with, at the same time, decreased amounts of sugar in the urine. We agreed that this gave added credence to the theory that the renal threshold for glucose is in some way influenced by pituitary activity.

The amount of glomerular filtrate is known to be tremendously in excess of the actual urine excreted, being 50 to 200 times greater,[20] depending on the amount reabsorbed by the tubules. It is known to vary only under certain unusual conditions. Richards has shown that in frogs only a certain number of glomeruli function at any one time. Under the action of adrenalin all but 5 per cent may close down temporarily and under caffein they may all open and function simultaneously.[21] Changes in blood pressure and blood flow through the glomeruli alter the amount of filtrate to some degree but on the whole there is surprising constancy. Even during water diuresis[20] the amount of glomerular filtrate remains essentially unchanged and, as in our experiments, with a daily fluid intake neither inadequate nor excessive and with the patient at rest on the ward, the amount of glomerular filtrate probably was more or less constant.

The amount of fluid reabsorbed by the tubules does vary enormously under ordinary diuretic or anti-diuretic influences. The anti-diuretic action of pitressin in man, for instance, is due to a local stimulation of water reabsorption in the thin segment of the loop of Henle.[6] Similarly, water diuresis depends on lessened reabsorption.* The modern conception of diuresis suggests hormonal control of tubular function even to changing the iso-electric point of the tubules.[21]

The tubular function of reabsorbing sugar is, in average human beings, well in excess of the maximum demands. The question arises as to whether, in an individual with a low renal threshold, this tubular function can be shown to be constant or variable.[23] Our evidence is incomplete but points to variation. Thus we see that when fluids are suddenly restricted the urinary output falls as does the sugar output. In the succeeding days the fluid intake and output remain constant but the sugar increases steadily until the usual level of sugar in the urine is reached. This can occur by a gradual daily increase in the amount of glomerular filtrate or by a gradual reduction in the reabsorptive function of the tubules for glucose. The current belief is, as Poulsson[5] said, that the glomerular filtrate remains fairly constant, and even if we try to explain the rise from 25 gm. to 77 gm. by change in amount of glomerular filtrate, there would have to be an unheard-of three-fold change with, at the same time, a three-fold increase in water reabsorption. Thus we are forced to conclude that the change occurs in the glucose reabsorptive function of the tubular cells. This problem was considered by Poulsson in working with phlorhizin. He says: "It has been a matter of some dispute (Loewi,[12] and Weber[21]) whether a superimposed diuresis increases the sugar elimination in phlorhizin diabetes. This, of course, depends on whether the extra diuresis is accompanied by changes in the rate

* In the experiments reported in this paper variations in amount of urinary sugar took place at times independently of any change in amount of urine (figure 5) although on restricted fluids the daily urine output was constantly somewhat in excess of the expected amount. During the period of salt free diet the water output was increased but the sugar output was decreased (figure 7) showing that these two substances vary independently of each other. This was apparent also during the pituitrin anti-diuretic test when the decrease in urinary output was accompanied by no comparable change in glycosuria.

of filtration through the glomeruli or not. When the filtration is augmented, e.g. by raising the pressure in the renal artery in the heart-lung-kidney preparation (deBoer and Verney) the amount of sugar in the urine is also increased; if the rate of filtration remains very constant, as is the rule normally, the sugar elimination like the urinary content of inorganic sulphate and creatinine is independent of variations in the volume of water excreted. Figure 3 (Exp. 3) illustrates this point." *

In his experiments the calculated amount of reabsorbed glucose varied independently from the amount of urine or the amount of reabsorbed fluid or the height of the blood sugar. Our patient is, in some respects, similar to a partially phlorhizinized individual. During xylose clearance tests the tubular reabsorption of glucose (tables 2 and 4) seemed to vary in proportion to the percentage of glucose in the glomerular filtrate rather than in proportion to the absolute amount of glucose filtered. That is to say, less glucose was reabsorbed from the more dilute filtrate with the result that, probably by chance, the same amount of glucose reached the bladder urine in each period. Thus we see that tubular function of reabsorbing glucose does vary once the threshold level has been passed.† These changes point to control of the function of the tubular cells and the analogy to the antidiuretic hormone is obvious.

Summary

We have reported observations on a patient with a very low renal threshold for glucose. It is apparent from our studies that water balance is an important factor in controlling the amount of sugar which appears in the urine in any 24 hour period although it has no effect on the total amount of sugar excreted over a long period of time. Sudden increase in fluid intake (forcing fluids) washes out large amounts of sugar and during

* Poulsson's Figure 3:

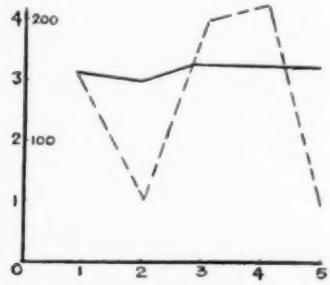

Fig. 3. Ordinate: - - - - - - - - - c.c. of urine per hour.
——————— g. glucose excreted per hour.
Abscissa: time in hours. (After Poulsson)

† In his book published October 1937, Homer Smith [24] reports unpublished experiments by Fisher and Shannon which, he says, demonstrate that in dogs once the threshold has been passed the kidneys maintain a constant rate of glucose reabsorption which is 200 mg. per minute and that all the filtered glucose in excess of this amount is excreted in the bladder urine. The protocols of these experiments are not presented, but the conditions of the acute experiment seem to be outside physiological limits ordinarily encountered.

periods of starvation, as after surgical operations, this leads to acidosis and should be avoided.

Certain data are needed to elucidate the kidney tubular activity which determines the renal threshold. The fact that the renal threshold varies during pregnancy, taken in conjunction with our observations, suggests hormonal control similar to that exerted by posterior pituitary extract on the renal tubules.

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THE IMPORTANCE TO THE INTERNIST OF LATENT PARANASAL SINUSITIS *

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PARANASAL sinusitis in its focal infective aspect has received considerable and merited attention in the last 15 years. The acute and chronic suppurative conditions, with pain, febrile course, frontals or antra opaque on transillumination, pus pouring from ethmoid-sphenoid region or copious purulent washings from an antrum, are easily recognized, and, in general, well handled.

Chronic hyperplastic sinusitis, on the other hand, is for the more part a milder condition whose usual manifestations are neither pronounced nor dramatic. The relationship of this lesion to asthma has been emphasized by Cooke.[1] We propose to discuss the part played by some of its milder forms in certain general disturbances and to call attention to the fact that its subjective local or rhinological manifestations may be slight or even nil; that diagnosis must be made by the internist; and that perseverance in treatment meets with a fair measure of success.

The predominance of general symptoms over local or head symptoms usually brings this case to the internist instead of the rhinologist, and because the objective findings and head symptoms are slight or do not trouble the patient at all, and because no suppurative condition can be demonstrated, some persuasion is ordinarily required to induce the specialist to display much interest.

The patient complains of aches and pains in varied regions of the body, and it is often impossible to determine whether these sensations have their origin in muscles, nerves or joints. Almost all complain of fatigue. A few show some slight temperature disturbance. Some are asthmatic. Chronic cough and morning clearing of the naso-pharynx are common. A considerable number have rather frequent colds, and we have come to feel that the incidence of two or more colds a winter is very suggestive of chronic sinus disease. The subjective symptoms of this group on the whole are general in nature and therefore they consult the general practitioner or the internist.

Examination shows congestion of nasal and pharyngeal mucous membranes; the turbinates may be swollen, or the septum deflected. The pharynx is solidly congested or shows a streaked appearance. It may be covered by a muco-purulent coating significant of discharge from posterior

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ethmoids and sphenoids. The tonsils if present are unhealthy, and the anterior pillars are injected.

This is the general picture of what may be termed "latent sinusitis," and the diagnosis of sinusitis should be made on the basis of such history and physical findings. Its more exact localization may be left to the roentgenologist and the rhinologist.

The real difficulties to be encountered arise at this point. If the patient is sent for roentgen-ray examination, the stumbling blocks are likely to be poor position in making the films and then poor interpretation. The films do not give good ethmoid or sphenoid exposures, or they are too hard, showing the bony structures, but not the soft tissues. Again one often receives negative interpretations of what are obviously positive findings, so that we are in the habit of interpreting films for ourselves, insisting always on seeing them, and never accepting a mere written or verbal report.

The next difficulty apt to arise is with the rhinologist. A case which does not reveal pus pouring from some of the posterior group of sinuses, or frank purulent discharge on washing an antrum, is regarded as having no demonstrable sinus disease, and word comes back that there is nothing for the specialist to do. Or if he does find ethmoid or sphenoid disease he tells the patient that nothing worth while can be done about it and he had better save his money.

TABLE I

Subjective Symptoms in 100 Consecutive Cases of Antrum Infection
Suppurative type 51
Hyperplastic type 49

General		Local	
Lassitude	82	Discharge	77
Repeated colds	63	Pain (head)	61
Rheumatic pains	50	Obstruction	11
Cough	36	No local subjective symptoms	16
Indigestion	33		
Loss of weight	23	*Of this last group of 16*	
Asthma	14	Suppurative type	5
Hay fever	8	Hyperplastic type	11

* * * * *

Table 1 shows the typical subjective symptoms and their relative incidence in 100 consecutive cases with antrum infection, both suppurative and hyperplastic. This particular sinus (the antrum) was selected for study and discussion because of its easy demonstrability by transillumination and by roentgen-ray, and because the use of lipiodol serves to give a graphic idea of the degree of thickness of the mucous membrane and the change which occurs in it under treatment. It is to be understood, however, that all that we say here regarding antral infection applies with equal force to ethmoid and sphenoid cases.

The striking thing in this table is that 16 of the entire group, 11 of which were hyperplastic cases, had no subjective symptoms referable to the

nose and throat, and that all of them consulted the internist first, on account of generalized symptoms such as lassitude, rheumatic aches and pains, indigestion, etc. Local treatment by the rhinologist was the chief, if not the sole, measure employed in treatment and resulted in relief of symptoms in each case.

Four typical cases have been selected from the hyperplastic group of 11 and are reported herewith.

Case Reports

Case 1. Complains of lassitude for two years, lumbar pain the past eight months and 15 lbs. loss of weight in six months. There are no subjective complaints referable to the nose and throat.

Roentgen-ray shows a moderately cloudy right antrum. Washings from the antrum are grossly clear, centrifuged and examined microscopically; there are many epithelial cells with cast off cilia. No leukocytes.

Culture: two colonies *Staphylococcus albus.*

Lipiodol injected into the antrum shows a tremendous thickening of the mucous membrane. Blood: slight polymorphonuclear leukocytosis.

Treatment over a period of two months consisted of three irrigations of the antrum, three lipiodol instillations, and five argyrol or cocaine packs. At the end of two months' treatment the lipiodol injection of the antrum showed a mucous membrane of normal thickness. Follow up (four months after treatment was begun): No pain for two months; no fatigue for three months; gain eight pounds in weight (figure 1).

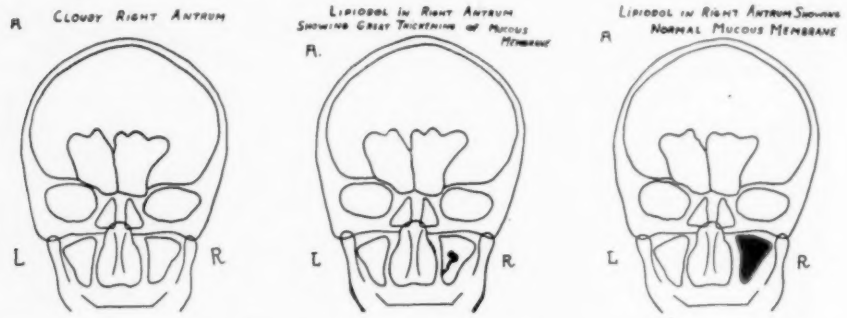

FIG. 1. Diagrammatic illustration of Case 1, before treatment and after six months treatment.

The lipiodol shadows are drawn as nearly as possible to the outlines of the roentgen-ray shadows.

The diagrammatic scheme is employed in preference to photographs of the actual films because of its simplicity and to avoid the lack of detail and consequent confusion which the photograph of the film involves.

Case 2. Complains of marked lassitude the past six years and frequent colds the past four years. No local subjective symptoms.

Roentgen-ray reveals a hazy left antrum, and lipiodol injection shows a very distinct thickening of the mucous membrane. Washings from the left antrum clear, microscopic examination of the centrifuged specimen showed no cells, and culture was sterile. Blood showed a slight polymorphonuclear leukocytosis. Treatment was over a period of five months and consisted of six irrigations of the left antrum, one lipiodol instillation, and 12 argyrol or cocain packs. Roentgen-ray with lipiodol toward the

end of that period showed normal mucous membranes. Three years later: there had been no fatigue in that time, and very few colds. (Figure 2.)

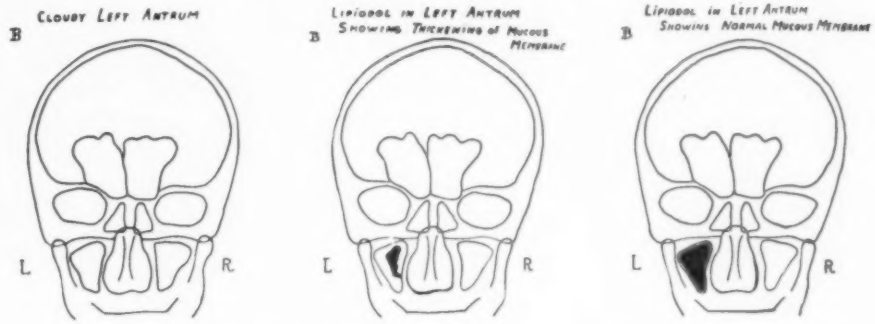

FIG. 2. Diagrammatic illustration of Case 2, before treatment and after five months treatment.

Case 3. This patient had experienced abnormal fatigue for five years, and for past two months was troubled with pain in the right hand and in the lumbar muscles. A cloudy left antrum was shown on roentgen-ray, which filled very poorly with lipiodol, showing a mucous membrane almost a quarter of an inch in thickness. Washings from the left antrum were clear. Microscopic examination: A few leukocytes and ciliated epithelial cells. Culture sterile. Blood: Polymorphonuclear cells very immature—pronounced shift to the left. Treatment over a period of two months consisted of six irrigations and two lipiodol instillations. At the end of this time lipiodol roentgen-ray film showed a mucous membrane of normal thickness. The patient was completely relieved of fatigue and pain and was still without symptoms two years later. (Figure 3.)

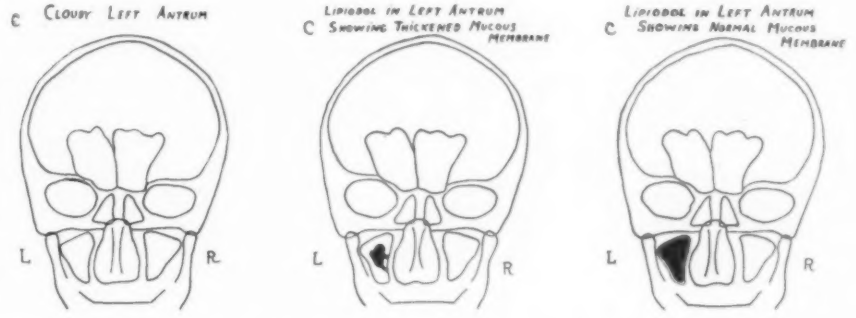

FIG. 3. Diagrammatic illustration of Case 3, before treatment and after two months treatment.

Case 4. This patient complained of sciatic pain and dry cough for the past four months. He had suffered undue fatigue for five months.

The left antrum and left anterior ethmoids were cloudy on roentgen-ray and with lipiodol the antral mucous membrane was shown to be between ⅛ and ¼ inch in thickness. Washings were clear: centrifuged and examined microscopically showed fragments of epithelium, ciliated cells and cholesterin crystals. Blood showed a large percentage of immature neutrophilic leukocytes. Treatment over a period of two months comprised two irrigations of the left antrum, two lipiodol instillations, one ephedrine displacement, and six argyrol or cocain packs.

Roentgen-ray with lipiodol at the end of that period showed a mucous membrane of normal thickness. Follow up six months after treatment was begun: no pain or cough and no fatigue. (Figure 4.)

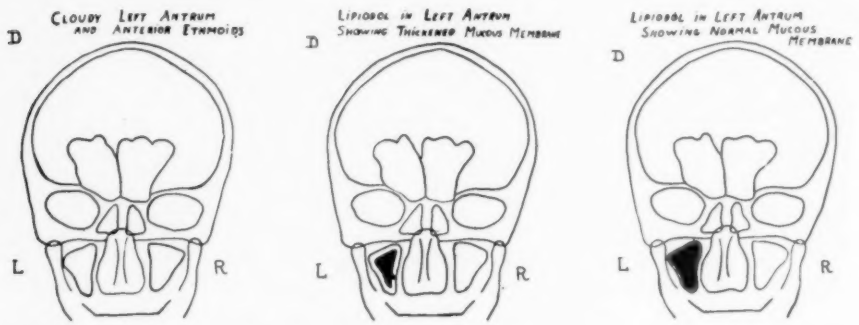

FIG. 4. Diagrammatic illustration of Case 4, before treatment and after two months treatment.

DISCUSSION

It will be noted: First, that the complaints of these patients are of lassitude, and lumbar or sciatic pain. One had frequent colds, but not one complained of obstructed breathing, excessive nasal secretion, or head pain.

Second, antral cloudiness and a considerably thickened mucous membrane on lipiodol injection were demonstrated by roentgen-ray.

Third, washings from the antrum in all cases were grossly clear and in three cases sterile on culture, while in Case 1 two colonies of *Staphylococcus albus* were grown, which were probably contaminations.

Fourth, that conservative treatment over a period of two months in three cases, five months in the fourth, resulted in shrinkage of the antral mucosa to a normal thickness, and great if not complete relief of fatigue and rheumatic symptoms. A gain of 8 lbs. weight resulted in one case (Case 1) and freedom from colds in another (Case 2). The follow up data extended over periods ranging from six months to three years.

An important question arises here. If the washings from these antra were sterile, what was the pathology and the origin of symptoms in these cases?

We believe that there is a direct analogy between infection in this locality and that in the gall-bladder. It has been recognized for some years that the important locus of gall-bladder infection is not on the surface of the gall-bladder mucous membrane, but in the submucosa itself.[2]

The same thing has been reported by R. A. Cooke [1] in regard to antrum infection, and we have verified this by taking the mucosa excised at radical antrum operations (Caldwell-Luc method), sterilizing the outside with iodine and alcohol, grinding up the mucosal segment and growing pure cultures of bacteria therefrom.* It seems probable that in the chronic cases

* It is to be noted that, in the cases whose tissues were thus examined, surface cultures made prior to operation were sterile, as were the surface cultures made at the time when the membrane was removed at operation.

the bacteria have become well imbedded in the body of the mucous membrane, where they may lie for some time dormant as far as any surface expression of their presence is concerned (that is, secretion), but elaborating toxins, which, getting into the blood stream, produce symptoms in distant parts of the body.

This is the type we term "latent" sinusitis, and all that has been said above applies with equal force to the infections of the ethmoid and sphenoid cells. The later, however, are not so accessible to roentgen-ray demonstration as the antra, because it is difficult to retain lipiodol in them for the making of films, and therefore we have confined our demonstration to antrum infections. It must be emphasized too that conservative treatment of the posterior group of cells, directed toward improving drainage by shrinking down the nasal tissue, is quite as satisfactory as in the cases described.

The importance of the whole subject lies in this: The diagnosis must often be made by the internist, whom these patients as a rule consult before anyone else; or they come to him having been told by the rhinologist there is nothing to be done, or that he has done all he can. Having convinced himself of the diagnosis the internist must insist on treatment being instituted and carried on for a sufficient length of time. It requires patience and persistence, but has its reward, and quite frequently results in relieving symptoms which have been bothersome and crippling for months or even years.

Conclusions

There may therefore be an infected mucous membrane which produces little or no discharge for varying periods of time, but is, nevertheless, quite capable of causing focal or generalized symptoms. Evidence of such a condition may be obtained from the patient's history, the presence of congestion or swelling of the nasal mucosa, and departure from the normal on roentgenological examination, which must be accurately made and carefully interpreted. The presence of such infection once established, prolonged treatment and patient handling must follow to insure results. Radical procedures are rarely needed in the class of case here presented.

Summary

1. A type of infection of the paranasal sinuses is discussed in which the pathology consists of a hyperplastic inflammation with the bacteria imbedded in the submucosa *without* surface discharge, but with a greatly thickened mucous membrane, as demonstrated by roentgen-ray with lipiodol injection.

2. The patient's complaints are largely of a general type and very little directly referable to the nasal passages.

3. A table is offered showing the incidence of symptoms, general and local, in 100 consecutive cases of antrum infection of both suppurative and

hyperplastic types, and it is emphasized that of the entire group 16 per cent had no local subjective symptoms whatever.

4. Four of these cases are reported, demonstrating: (*a*) absence of local subjective symptoms; (*b*) positive roentgen-ray findings with lipiodol; (*c*) negative antrum washings; and (*d*) improvement under treatment.

5. It is important that diagnosis of this type of case should be made by the internist, on the basis of history, presence of local signs and abnormal findings on roentgen-ray.

6. Sphenoid and ethmoid infections exhibit the same characteristics as the antral cases, the latter being employed for this study because of their greater ease of demonstration by transillumination, roentgen-ray, etc.

7. Prolonged and careful treatment is essential, and radical procedures are seldom required.

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ACUTE INSUFFICIENCY OF THE ADRENAL GLANDS; REPORT OF 2 CASES *

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The syndrome of chronic adrenal insufficiency has received considerable attention in the literature in the past decade due to increased knowledge of the pathologic physiology and improvement in therapeutic methods.[1, 2, 3] Acute failure of adrenal function, beyond those cases noted in the new born as a result of trauma or hemorrhagic disease, is an uncommon finding.

Reports of cases of acute insufficiency of the adrenal glands have appeared in the literature. The earliest such case noted is Case 10 in the original paper of Addison.[4] This case is not so typical as many of the other subsequent reports. Addison's case was in a 28-year-old female with cancer of the uterus who died four days after admission. At necropsy she showed pigmentation of the skin. "Although the right adrenal was intact, the left had a malignant tubercle which had developed at that precise point where the large vein escapes from the organ; this tubercle projected into the interior of the vein, so as almost or entirely to obstruct it, and had, moreover, led to rupture and effusion into the capsule itself." This case of advanced malignant disease came to an acute termination with a sudden hemorrhage into the gland secondary to a metastatic focus occluding the vein. The apparently intact right adrenal was incapable of supporting life.

Since then there have been sporadic reports of cases of this type. Lavenson [5] in 1908 reported one such case due to thrombosis of the suprarenal veins with hemorrhagic necrosis of both capsules. Lavenson felt that the degree of tissue destruction was in no way a measure of functional incapacity but when such destruction reached a certain degree, or involved certain elements, clinical signs were manifested.

Boyd [6] describes a 38-year-old soldier who had been quite active. He was found unconscious in his room and was taken to the hospital where he died two and one-half hours after admission. Autopsy revealed old fibrotic tuberculosis of the apices of both lungs with a cavity the size of a hazel nut at the right apex. There was complete obliteration of both pleural cavities by firm adhesions. Except for small islands of cortical tissue in the left adrenal there was complete replacement of both adrenal glands by structureless amorphous acidophilic tissue which showed caseation necrosis, numerous endothelial cells and giant cells. No recognizable medullary tissue was present.

Several other reports are found in the literature of relatively sudden

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death after minor illnesses, trauma or operative procedure in which on autopsy extensive tuberculous disease of the adrenals was found. Oudard [7] reported a case of a male, aged 42, who developed mild asthenia following an accident. After an operation for non-union, he went into coma and died. The adrenals were completely replaced by large confluent tubercles. Terzani [8] observed a young male adult who after a three-day influenza-like illness at home was admitted in coma. His previous history was irrelevant in all respects. After admission he became violent, incoherent and incontinent. There was slight pigmentation of the skin with pigmented areas of the palate, penis and scrotum. Death took place in 24 hours. Section showed bilateral caseation of the adrenals, the peripancreatic and periaortic nodes. The apex of the left lung showed a fibrotic lesion surrounded by a few areas of caseous pneumonitis. Cohoe [9] reported a case in which death occurred in five days following vascular changes in the adrenals.

Case Reports

Case 1. J. McD., aged 41, male, married salesman, admitted in coma April 5, 1935, 4:50 p.m. and died four and a half hours later. History was obtained from wife. His father died of malignant disease of the throat, his mother was living and well. There were no siblings. The previous history revealed pleurisy, emphysema, pneumonia and measles. The time relationship of these illnesses was unknown. At the age of eight he had right hip disease. This joint became stiff and for the past eight years there was a discharging sinus over this joint. Last year he had "neuritis" of his shoulders and arms. He had been married for 15 years. There were two children living and well. In 1923 his wife had a spontaneous miscarriage. The deceased had always been a heavy smoker and was a heavy drinker at intervals. For an indefinite period he had been losing weight, tiring easily and showing some darkening of the skin. He remained at his work, never losing any time.

On the day prior to his admission he drank heavily but was able to drive his car home. His wife did not hear him enter. In the morning he could not be aroused. Respiration was stertorous. On the advice of the family physician the patient was hospitalized that afternoon. On admission the patient was in coma and could not be aroused. Breathing was noisy and irregular. There was evidence of loss of weight. The skin showed scattered areas of brownish pigmentation more marked over the scrotum. The pupils were equal and reacted to light. The nose and ears were negative. The lips were cyanotic. The throat could not be visualized because of inability of patient to coöperate in opening his mouth. There was no neck rigidity No peripheral lymph nodes were palpable. The chest showed good resonance. Coarse moist râles were present throughout. The heart sounds were regular, but the details were masked by the noisy respiration. The abdomen was held rigidly. No viscera or masses were palpable. The right lower extremity was smaller and shorter than its fellow. There was a draining sinus tract on the anterior aspect of the right hip. There was no edema.

Course: On admission the temperature was 101.6° F.; pulse 94, respirations 20. Blood pressure 110 systolic, 80 diastolic. Hemoglobin 82 per cent. Red blood cells 4,600,000; white blood cells 10,400. Polymorphonuclear leukocytes 66 per cent. Lymphocytes 34 per cent. Urine: albumin: trace; sugar: negative; acetone: one plus. Blood chemistry: urea: 16.7 mg. per 100 c.c.; creatinine: 1.43 mg. per 100 c.c.; glucose: 62.0 mg. per 100 c.c. Wassermann reaction negative. Coma deepened rapidly and patient died 4½ hours after admission.

Autopsy Findings

Section performed 13½ hours after death. The right lower extremity was four inches shorter than its fellow. There was marked decrease in circumference at all levels. The limb had a shriveled, wasted appearance. Just below the lateral end of

Fig. 1. Gross appearance of adrenals. The right adrenal, above, has been split laterally; the left, below, in a horizontal plane.

the inguinal ligament there was a two-inch vertical scar. The proximal part of this was separated, red in color and covered by inspissated pus. There were 10 old depressed stellate scars scattered about the anterior lateral and posterior aspects of the hip region. The skin of the ventral surface of the body was darker than the dorsal

surface. This pigmentation was more marked about the scrotum. A triangular patch of pigmentation was noted on the left side of the buccal mucosa. The scalp hair was abundant but gray-streaked. The left supraclavicular fossa was deeply retracted. The trachea was slightly deviated to the right.

Examination of the thorax showed a smooth right pleura except for a line of firm adhesions binding visceral and parietal layers. This line exactly followed the interlobar fissure separating the right upper from the middle lobe. The left pleural cavity was completely obliterated. Every part of this lung was so intimately adherent to the thorax that the lung was removed from the chest with considerable difficulty. The lungs were intensely congested and edematous. There was no scarring of the apices or cavitation. At the apex of the left lower lobe just beneath the pleura was a small,

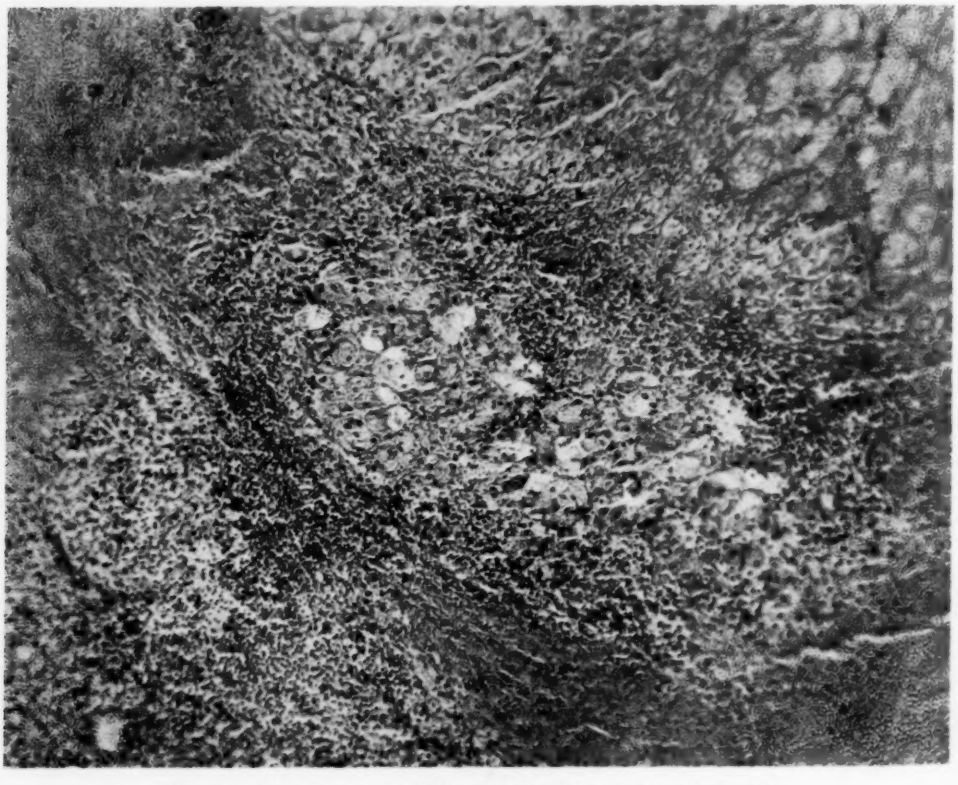

FIG. 2. Low power (× 200) showing island of cortical cells.

hard, encapsulated nodule measuring 1 by 0.5 by 0. 5 cm. On section there was a hard cortex with a soft, cheesy, white center (Kuss-Ghon primary complex).[10] There was a moderate dilatation of the bronchi and bronchioles of the left lower lobe. The trachea and peribronchial lymph nodes were enlarged, firm and on section were gray with mottled black central areas.

The pericardial sac was completely obliterated by dense firm adhesions. The left pleura was adherent to the pericardium. Over the anterior aspect of the heart at the base there was one area about one and a half cm. in diameter which was bony in consistency. The heart weighed 270 grams (in spite of the adhesive pericarditis, the underlying lesion resulted in a small heart). The chambers, valves and valve orifices

were average. There was a minimal degree of atheromatosis of the coronary arteries and of the aorta.

The abdominal viscera were in average relationship. No fluid was present in the cavity. The gross appearance of the liver, spleen, pancreas, kidneys, bladder and prostate was not noteworthy. The gastrointestinal tract showed no ulcerations or scarring. There were a few caseous and calcified nodes of various sizes at the root of the mesentery.

The adrenal glands were appreciably larger than usual. The left measured 4 by 3 by 2 cm.; the right 4 by 4 by 2 cm. Both capsules were firm and nodular. The cut surface was grayish white in color with many irregular soft caseous areas. Throughout both glands there were occasional islands of chrome yellow tissue.

Head: No trauma of the scalp. The vault and base of the skull were intact. The accessory nasal sinuses, middle ear and mastoid were normal in appearance. There was moderate edema of the brain. Section after fixation showed no noteworthy variations. The venous sinuses of the dura were smooth walled throughout.

Histologic sections of the skin show dopa-positive cells in the corium. The adrenal glands were almost completely replaced by large confluent areas of caseation necrosis with frequent Langhans' giant cells. There were scattered foci of recognizable cortical cells. These showed vacuolated cytoplasm. The primary pulmonary complex showed a well encapsulated caseous area surrounded by a zone of lymphocytes. There were several areas of fibrosis in the right upper lobe.

A purulent bronchitis was present in the left lower lobe. Moderate cloudy swelling and granular degeneration were present in the hepatic cells. There were several scattered areas throughout the liver consisting of endothelial cells and lymphocytes surrounding a small necrotic center. These tubercles were all of approximately equal size. The spleen, kidneys, prostate and bladder showed no significant abnormalities. The aorta showed minimal intimal atheromata. The base of the heart showed calcification beneath the adherent pericardium. No amyloid changes were present in any organ.

Anatomical Diagnosis: Tuberculosis of the adrenals; primary infective complex, in apex of left lower lobe; caseous tuberculosis. Tracheal and peribronchial tuberculous lymphadenitis; mesenteric tuberculous lymphadenitis; miliary tuberculosis of the liver. Tuberculosis of the right hip joint; obliterative pleuritis (left); obliterative pericarditis; calcification of the pericardium.

Case 2. M. N., aged 21, single, had no complaint until 48 hours before admission when he went to bed complaining of an aching feeling in lower extremities, but his mother stated that he frequently had the same complaint because of his occupation as a shipping clerk. On February 2, 1938, he awoke and complained of a headache and generalized pains over his body. He went to work but had to return home because of a severe headache and a feeling of weakness. On arriving at home he vomited. The vomitus did not contain blood. That evening he vomited twice. The following morning, February 4, 1938, he arose and still complained of headache, and in addition his mother noticed that his speech was thick and difficult to understand. Patient became irritable, wanted to be left alone and then would demand things in a very irritable tone of voice. He responded to questions only after his mother would scold him and then in a thick voice which was difficult to understand. He did not vomit any more but felt nauseated. A physician was called and found that he had a temperature of 106° F. and advised hospitalization. He was admitted on February 4, 1938, at 8:04 p.m. in a semicomatose state, irrational and uncoöperative; extremities were cold and clammy. Respirations were normal and the temperature was 105.2° F. The only positive findings were rigidity of the neck, tachycardia, no blood pressure obtainable, pulse imperceptible, extremities cold and knee jerks were absent. No other neurological signs were present.

A spinal tap was performed—15 c.c. of clear fluid obtained—under a pressure of

16 mm. of mercury. There was a positive Queckenstedt. About one-half hour after tap the respiration became irregular and five minutes later, stopped entirely. The heart sounds were heard for a few minutes and then were no longer heard. The patient expired at 10:08 p.m., two hours and four minutes after admission. The blood chemistry was as follows: N. P. N.: 91.0; urea N 52.0; creatinine: 2.2; glucose: 107.0; urea ratio: 56.0. Urine: specific gravity: 1.009; albumin: 2 plus; leukocytes: 20–25 per high power field and numerous finely granular casts.

Autopsy Findings

Section performed 10 hours after death. The body was that of a young adult male, 5 feet 10 inches in height and well developed and muscular. There was a moderate diffuse dependent hypostasis. There were no evidences of external injury.

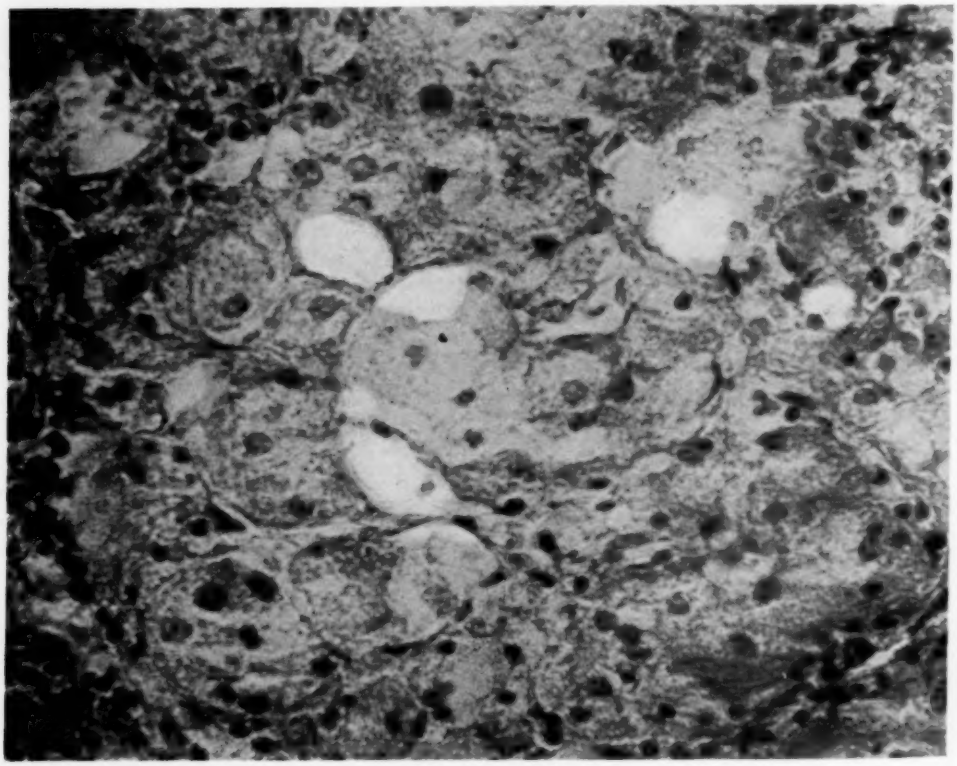

Fig. 3. Illustrating hydropic changes in cortical cells.

There were no scars. The hair of the scalp was brown and abundant. The pupils were markedly dilated and irregular. There were marked subconjunctival hemorrhages of both eyes. There were no palpable lymph nodes noted. There was no peripheral edema, nor were the fingers clubbed.

There was no free fluid in any of the serous cavities. Examination of thorax showed voluminous lungs which were deep mahogany brown in color with interspersed purplish areas. On section bloody frothy fluid was expressed from all surfaces. There were no areas of consolidation. The trachea and bronchi were filled with pink frothy fluid. The mucosa of the bronchial tree was smooth throughout. The

branches of the pulmonary artery within the lung parenchyma were smooth walled. On search, no primary infective nodule could be demonstrated. There were no significantly enlarged tracheal or peritracheal or mediastinal lymph nodes. The heart, which weighed 370 grams, showed numerous subepicardial hemorrhages. The valves were smooth, translucent and showed average appearances throughout. There were no changes in the myocardium. The aorta was normal in circumference and smooth walled. The coronary vessels were smooth walled throughout. Both superior and inferior venae cavae showed no evidence of thrombosis. The liver was smooth walled and glistening, was deep mahogany brown in color and on section showed a diffuse nutmeg appearance. The biliary system was normal throughout. The pancreas was normal in appearance. The spleen showed no abnormalities. The gastrointestinal tract was smooth walled throughout and showed no scars or tumors. The kidneys combined weighed 280 grams and were flabby in consistency. The capsule stripped with ease. There were numerous small surface hemorrhages. On section the cortex was clearly demarcated from the medulla and of average width. There were no hemorrhages on section. The pelves was smooth walled. The ureters and bladder were normal in appearance.

The adrenals were embedded in a large amount of fat tissue and felt solid on palpation. The right adrenal was divided into two roughly equal halves by firm scar tissue, one portion measuring 3.5 by 2 by 1 cm., the other 2.5 by 1.5 by 1 cm. On section the cut surface was homogeneously yellow in color and resistant. There was an irregular zone of hemorrhage peripherally, in both portions. There was no grossly recognizable adrenal tissue. The left adrenal was irregularly oval in outline measuring 4 by 3 by 2 cm., firm in consistency and resistant to section. The cut surface was homogeneously yellowish white in color.

Head: There were no scars or hematomas of the scalp. On removal of the calvarium, no fractures of the vault or base of the skull were found. The brain was markedly congested, but no exudate or hemorrhage was present. Section of the brain after fixation showed no areas of hemorrhage or tumefaction. The ventricular system was normal. The pituitary was average in size.

Microscopic: Histologic sections of the adrenals showed extensive caseation throughout, surrounded by irregular zones of lymphocytes with irregular endothelioid cells and with not infrequent Langhans' giant cells. Sections from the left adrenal showed no recognizable cortical or medullary tissue. There was a focal lymphocytic infiltration in the surrounding fat. The right adrenal showed several irregular areas of recognizable cortical tissue, the superficial layers of which showed pyknotic nuclei. The cytoplasmic outlines were obscured. In the deeper layers there was marked cloudy swelling and granular degeneration of these cortical cells. Irregular lymphocytic infiltration was present in this cortical tissue.

Sections from other organs showed no significant changes. There was no evidence of tubercle formation in any of the other viscera.

Anatomical Diagnosis: Bilateral tuberculosis of the adrenal glands.

Comment

The first case presented showed extensive obliteration of the suprarenal capsules by a caseating process associated with a childhood form of tuberculosis, with tuberculosis of the right hip joint. There were several remnants of cortical tissue scattered through the caseous areas. These islands of cortical tissue were apparently sufficient to enable him to keep at his daily work as a salesman. It was not until a heavy drinking episode took place that acute failure ensued. There was some functional incapacity as shown by skin pigmentation, loss of weight, fatigability and asthenia.

In the case reported by Terzani [8] the precipitating factor was an upper respiratory infection. Here too, an almost completely obliterated pair of adrenal glands were able to carry on life, but an additional load, here an acute infection, " broke the camel's back."

In this connection the observation of Sezary [11] is of note. He states that 90 per cent of the adrenals can be destroyed without fatal issue, or without apparent clinical signs. To be sure, the functional capacity of such a gland has little or no reserve and any undue, unusual or increased demand is met with a sudden collapse. Boyd [6] states that similar cases of acute insufficiency are seen with anatomically intact adrenals but with degeneration of other chromophil tissue and abdominal sympathetic ganglia. It is noteworthy in this connection that in tuberculosis sanatoria, tuberculous disease of the adrenals is not infrequently discovered at autopsy. These cases have no clinical evidence of Addison's syndrome. The histologic picture of the glands shows varying amounts of cortical tissue. Lavenson [5] has described four clinical types of acute insufficiency of the adrenals: an acute abdominal form with vomiting and shock; a cerebral form with convulsions and coma; an asthenic form; and lastly a form with sudden death without premonitory warning. Both of our cases belonged to the cerebral type. It will be remembered that in the first instance the acute adrenal insufficiency followed a drinking bout. Chemical examination of the brain, however, revealed only a slight trace of ethyl alcohol.

Such cases as these have a medico-legal bearing. The importance of sudden death from such a progressive lesion must be considered. The first case at hand was considered as an alcoholic death until autopsy and chemical analysis were done; the second was thought to be due to meningitis.

Summary

Two cases of relatively sudden death are reported due to extensive tuberculous disease of the adrenal glands.

The cases reviewed in literature, as well as our two cases, have all shown devastating lesions in the glands with but small strands of cortical tissue. These glands were capable of carrying on until an extra functional load was experienced.

The possibility of acute insufficiency of the adrenal glands should be considered in medico-legal cases.

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STUDIES OF IRON METABOLISM IN A CASE OF HEMOCHROMATOSIS *

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IN connection with the clinical study and care of patients with hemochromatosis seen in this clinic,[1] it seemed desirable to investigate the iron metabolism by means of balance studies. This was thought particularly worthwhile because of the paucity of such data in the literature. Only four reports have come to our attention, namely those of Howard and Stevens,[2] McClure,[3] Dry [4] and Fowler and Barer.[5]

CASE REPORT

Mr. F. H. was first seen on August 2, 1933 when 47.6 years of age. Sugar had been found in his urine first in August 1931 and from his history it was estimated that the onset of the diabetes had been in January of that year. The symptoms at onset had been polyuria, polydipsia, polyphagia, and loss of weight and strength. The bronze color of his skin had been noted first in November 1931, and while under the care of the Lahey Clinic in January 1932, the diagnosis of hemochromatosis had been made and verified by a biopsy of skin (examined by Dr. Shields Warren, Pathologist to the New England Deaconess Hospital).

Family History. The patient's mother, who was 78 years old in 1933, was said to have had diabetes for 10 years. A letter from her family physician in 1936 indicated that she occasionally had glycosuria following dietary indiscretions but that otherwise the urine was sugar free. It may, therefore, he regarded as doubtful whether the mother really has true diabetes. The patient's sister, who in 1933 was 44 years old, has sugar in the urine at times, but a sucrose tolerance test was normal in 1933. A maternal uncle of the patient is said to have died from diabetes. The patient's father died of nephritis at the age of 77. The patient has no brothers and has one sister other than the one mentioned above; this second sister is living and well and in 1933 was 42 years old. The patient's wife is living and well. There is one child living and well who in 1933 was 23 years old. No relative of the patient has been known to exhibit signs or symptoms suggesting hemochromatosis.

Past History. Past illnesses included measles, mumps, and whooping cough in childhood and appendicitis at the age of 18 years. For years the patient had been troubled by chronic catarrh. Before prohibition he had drunk much beer for years, three or four bottles a day, but very little other liquor. Since prohibition he had had no beer but had had occasional whiskey highballs although never to excess. He had had practically no liquor since 1931.

Physical Examination. Physical examination during his first hospital admission showed the heart to be normal in size and regular in rhythm; a systolic murmur could be heard over the whole precordium. The lungs were clear. The abdomen was soft and non-tender although the spleen could be touched and the liver could be felt to descend on inspiration to the level of the umbilicus; it was hard in consistency. Pulsations could be felt in the dorsalis pedis arteries in the feet, and the patellar reflexes were equal and normally active. The blood pressure was 110 systolic, 70

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diastolic. There was slight pitting edema over the shins. Sclerosis of the radial arteries was graded as 3 on a scale of 4. The skin over the whole body had a queer brownish hue as if dirty; the arms and legs over the regions which had been exposed to the sun showed particularly the characteristic bronze color. The hair over the head and the axillary and pubic hair was scant. There was atrophy of both testes. (The patient stated that there had been a loss of sexual power and desire for three or four years.)

Laboratory Findings. The admission specimen of urine contained 10.8 per cent sugar and gave a 1 + reaction with ferric chloride. The specific gravity of the urine was 1.045, the reaction was acid, there was a very slight trace of albumin, and no bile. In the sediment there were no casts and an occasional red blood corpuscle and an occasional white blood cell per high power field of the microscope. The red blood count was 4,870,000, hemoglobin (Newcomber) 80 per cent, and white blood count 9,350 to 11,550. Examination of a stained smear showed no abnormalities. The blood non-protein nitrogen varied from 27 to 33 milligrams per 100 c.c. of blood. The blood cholesterol was 200 milligrams per cent. During a two-week stay in the hospital the fasting blood sugar varied from 0.18 per cent to 0.27 per cent. The blood bilirubin was normal, 0.2 milligram per 100 c.c. (monophasic reaction). The basal metabolic rate was plus 7 per cent. The blood serum protein was 6.0 per cent. A fragility test of the red blood corpuscles showed hemolysis to begin at a concentration of salt of 0.42 per cent and to be complete at 0.32 per cent. Urobilinogen in the urine was positive on two occasions in a dilution of 1 : 20, once in a dilution of 1 : 30, twice 1 : 50, and once 1 : 100. The bromsulfalein test of liver function showed no retention of the dye in the blood after 30 minutes. The blood calcium was 10.4 milligrams per 100 c.c. A roentgenogram of the chest on October 31, 1935 revealed nothing abnormal.

Course in Hospital. During this first two-week stay in the hospital in 1933 the patient's diabetes was gradually brought under control, and at the time of discharge his urine had been essentially free from sugar for five days on a diet of carbohydrate 201, protein 79, and fat 48 grams, 1552 calories per day and on 16 units of insulin before breakfast, 8 before lunch, 12 before supper, and 2 at bedtime.

Subsequent Course. The patient has been seen at fairly frequent intervals since the first admission both in the office and during hospital stays. The hospital admissions other than the first one were as follows: October 28 to November 2, 1935, October 25 to November 25, 1936, and October 3 to 9, 1937. There has not been a great deal of change in his condition during this time and in general he has held his own. The body weight without clothing at the end of the first admission was 119½ pounds (54.3 kg.) and at the end of the admission of October 1937 was 114 pounds (51.8 kg.). His health has been fairly good although his endurance and strength are by no means normal. The color of the skin has remained about the same. In October 1936 he was shifted to protamine zinc insulin and at the present time (January 1938) * his diabetes is under good control on 36 to 40 units of protamine zinc insulin once daily in the morning before breakfast. His present diet (so arranged in an attempt to maintain body weight) is carbohydrate 206, protein 73, and fat 116 grams, 2,260 calories daily. Examination of a single specimen of urine in October 1937 showed a specific gravity ranging from 1.010 to 1.020, a negligible amount of albumin, no bile, and in the sediment no blood, pus, or casts. A test for urobilinogen in the urine was positive in 1 : 30 dilution. The blood pressure was 128 systolic and 80 diastolic. A bromsulfalein test of liver function showed no retention of the dye at

* Note added March 22, 1939. The patient's condition has changed very little during the past year. His diabetic condition is kept under good control with 8 to 10 units of unmodified insulin and 40 units of protamine zinc insulin taken in the morning before breakfast. The liver is huge, the lower margin being felt upon inspiration at the level of the iliac crest. The spleen can be felt with the patient in the right lateral position.

the end of 30 minutes. A red blood count on October 9, 1937 was 4,320,000 and white blood count 9,600, hemoglobin 75 per cent, and the smear normal. The size of the liver and spleen has remained about the same. The liver descends 9 cm. in the mammillary line and crosses the abdomen at the level of the umbilicus. The spleen can just be touched with the patient in the right lateral position. A rectal examination reveals large external hemorrhoidal tags.

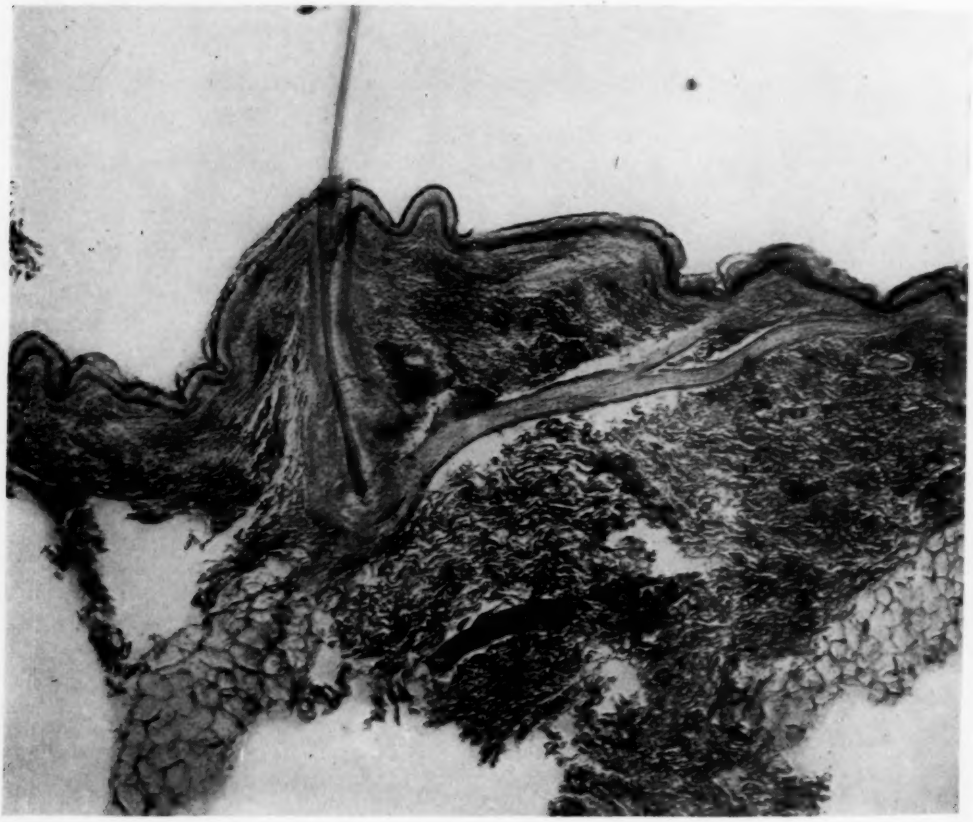

FIG. 1. Low power view of section of skin removed from Mr. F. H. Note the heavy deposit of melanin in the cells of the basal layer of the epidermis. Part, though not all, of the pigmentation in the rest of the section is due to deposits of iron-containing pigment. (Potassium ferrocyanide, counterstain 0.5 per cent basic fuchsin; × 48)

Laboratory data of a general nature which were collected in the hospital admission of October 25 to November 25, 1936 during which the studies of iron metabolism were carried out, are summarized herewith. The fasting blood sugar varied from 0.05 per cent (low because of an excessive dose of protamine zinc insulin) to 0.26 per cent. The blood non-protein nitrogen on one occasion was 27 and on another, 29 milligrams per 100 c.c. The urine contained little or no albumin and in the sediment there were no pus, blood or casts. The number of white blood cells varied from 6,200 to 10,150 per cu. mm. A tabulation of five differential counts on different days scattered through the month showed the percentage of neutrophilic leukocytes to average 49 and of lymphocytes, 44; otherwise the stained blood smear was not remarkable. A

phenolsulphonephthalein test of kidney function showed an excretion of 75 per cent of the dye in 2 hours. A bromsulfalein test of liver function showed no retention of the dye in the blood after 30 minutes. The blood bilirubin was normal, 0.3 milligram per 100 c.c. (monophasic). An alcohol test meal gave values for gastric acidity which if anything were somewhat above normal; the highest figure obtained for free hydrochloric acid was 98 points at 30 minutes after the alcohol had been given. No trace of gross blood was noted in the stools and although the benzidene test was reported as 1+, this lacks significance since the patient was not on a meat-free diet. A test of fragility of erythrocytes showed hemolysis to begin at a concentration of sodium chloride of 0.42 per cent and to be complete at one of 0.28 per cent. Biopsy of the skin was repeated and this again showed the presence of abnormal amounts of iron pigment, thus verifying the diagnosis of hemochromatosis.

FIG. 2. High power view of sweat gland seen in lower mid-portion of section shown in figure 1. Note the marked accumulation of iron-containing pigment. (Potassium ferrocyanide, counterstain 0.5 per cent basic fuchsin; × 300)

METHODS

The time of the experimental study was divided into nine periods of three days each (in the ninth period there were only two days). Preceding this, a five-day preliminary period on the diet outlined allowed time for adjustment to the diet and the ward routine. Balance studies were made on each three-day period and the iron con-

tent of the blood was determined at frequent intervals. During the month of study the patient was up and about and took daily walks but in general led a quiet life about the hospital.

Food Intake. The diet throughout the entire period of study was kept constant; not only was there no variation in the menu from day to day but as an added precaution the same preparations and brands—as of canned foods—were used from day to day. The dietary prescription was carbohydrate 230 grams, protein 73 grams, and fat 68 grams, furnishing 1824 calories per day.

The diet followed throughout the time of study is given in detail below:

	Grams		Grams
Asparagus	150	Bread	90
Peas	150	Uneeda biscuits	2
Tomatoes, stewed	150	Beef cube for bouillon	1
Beans, string	150	Chicken, sliced white meat	45
Potato, baked	180	Steak, broiled tenderloin	45
Orange juice	300	Egg, scrambled	45
Banana	100	Butter	25
Applesauce	140	Cream, 20 per cent	60
Oatmeal (dry weight)	15	Milk	360

The food was cooked either in aluminum or earthenware utensils and often served in the same vessel in which it was cooked. Distilled water was used for drinking.

Aliquots of food for analysis were taken on one day of each three-day period. One-fifth by weight of each article was placed in a large evaporating dish and sent to the laboratory. Of the seven food aliquots thus analyzed the maximum variation of iron content between any two lots was 4.2 milligrams. The average figure obtained by our analyses was 50.7 milligrams per three-day period. From figures given by Sherman [6] the calculated iron intake for a three-day period was 53.3 milligrams, a difference of only 2.6 milligrams from the figure obtained by analysis.

Collection and Preparation of Feces for Analysis. The feces for each three-day period were marked off by the appearance of carmine which was given to the patient each third afternoon at 3 p.m. With the exception of the first two periods, the results of which were averaged because of an error in the administration of the carmine, there was no difficulty in observing the end of each period. The carmine taken at 3 p.m. was always evident in the evacuation of the following morning. The feces for each day were collected in a large new enamel pail and sent at once to the laboratory where they were transferred by means of distilled water to a large evaporating dish which was kept on the steam bath, the entire feces for one period being all transferred to one evaporating dish.

After complete drying, which usually required three to four days, the entire mass was ground to a fine powder with mortar and pestle. Weights taken before and after grinding showed almost invariably a loss of not more than 1 per cent. There was never any difficulty encountered either in getting the material completely dry or in powdering. Five-gram portions of the mixed powdered material were taken for iron analyses.

Collection and Preparation of Urine for Analysis. The urine was collected in 24-hour quantities and sent to the laboratory where it was accurately measured, preserved with a known quantity of toluol and transferred to a carboy containing the urine for that period. The entire quantity was acidified with a known volume of hydrochloric acid, thoroughly mixed and sufficient of the mixed lot saved for analyses.

Reagents Used. All reagents used were as nearly as possible free from iron. Special iron-free hydrochloric acid was used throughout the experiment. The nitric

acid used contained according to analysis no iron to the fourth decimal place. The best sodium thiocyanate we could obtain was Baker's C.P. analyzed which contained according to analysis 0.00015 per cent iron. Five c.c. of a 20 per cent solution (the quantity used in the determination) made from this salt would theoretically contain then only 0.001 milligram. By actual determination 5 c.c. of a 20 per cent solution showed the barest perceptible tinge of color. Since both standard and unknown would be similarly contaminated any error from this source was considered entirely negligible.

Blank determinations were made using the same quantities of reagents as used in each set of analyses and in no case was sufficient color obtained to be readable against the weak standard.

The distilled water used came from a copper-lined distilling apparatus and was conducted through copper pipes to a glass carboy. A determination made on both 500 c.c. and 1 liter portions evaporated to dryness gave essentially negative results.

During the course of the experiment the laboratory was freed completely from any possible source of contamination. All glassware used was washed in 10 per cent hydrochloric acid before using.

The evaporating dishes used for the drying and ashing processes were of "sillimanite." They were guaranteed to stand a temperature of 1400° C. with no deleterious effect. Only at the very end of our analyses did any of the dishes show signs of any erosion and even then no discrepancy in results could be noted between determinations carried out on these slightly eroded dishes and new ones.

Chemical Methods. The method employed for the determination of iron was the Elvehjem procedure as modified by Farrar.[7] Known aliquots of material were covered with iron-free calcium carbonate and ashed in an electric furnace at a temperature of 500° C. ± 25°. The ashed material was extracted with hydrochloric acid, hydrolyzed in a hydrochloric acid solution and just enough concentrated nitric acid added at the end of the period of hydrolysis to insure complete oxidation of all iron to the ferric condition. The final solution was transferred to a volumetric flask, made up to a definite volume and iron determined colorimetrically according to the method of Kennedy [8] on a suitable aliquot. Two standards were used, one containing 0.1 mg. iron per c.c. prepared from pure ferrous ammonium sulphate oxidized with potassium permanganate according to Elvehjem and Hart [9] and another containing 0.01 mg. iron per c.c. prepared from the strong standard by dilution. Analyses were carried out always in duplicate and frequently in triplicate.

Analysis of Feces. All analyses on feces were made as outlined above by ashing 5-gram portions of the powdered material. Usually it was found necessary to ash a second time in order to obtain a satisfactory residue. In such cases the acid filtrates from each ashing were combined before hydrolysis and oxidation took place. The final solution in each case was made to a volume of 100 c.c. and usually 5 c.c. used for the colorimetric determination.

Analysis of Urine. Urine analyses were made on 500 c.c. aliquots of the acidified three-day sample. The urine was evaporated to dryness on the steam bath and the dried residue ashed as outlined above. One ashing was always sufficient to yield a homogenous light gray ash. The final hydrochloric acid solution was made to a volume of 100 c.c. and 20 c.c. used for the colorimetric determination. This quantity contained sufficient iron to be easily comparable with the weak standard containing 0.01 mg. iron per c.c.

Analysis of Food. The aliquot representing one-fifth of a day's diet was dried on the steam bath until no appreciable moisture was apparent. Then 75 to 100 c.c. of concentrated nitric acid were added in *small portions* until a homogenous yellowish mixture was obtained. The yellowish mass was evaporated until the volume became sufficiently small to permit easy transfer to a smaller evaporating dish. The larger

dish was washed out several times with small quantities of distilled water to which a few cubic centimeters of concentrated hydrochloric acid had been added, all washings being added to the original contents. Evaporation was then continued until the mass became quite dry. It was then covered with 2 grams of iron-free calcium carbonate and ashed. Two and sometimes three ashings were required to obtain a satisfactory residue. The acid filtrates were combined and made up to a volume of 250 c.c. For hydrolysis, 25 c.c. portions were diluted to about 150 c.c. and boiled 30 to 40 minutes or until the volume was reduced to about 10 c.c. at which point oxidation was brought about by the addition to the hot solution of a few drops of concentrated nitric acid. The oxidized hydrolysate was made up to a volume of 50 c.c. and 20 c.c. used for the colorimetric determination. Evidence that hydrolysis and oxidation were complete under these conditions was afforded by obtaining essentially identical colorimetric determinations on different hydrolysates produced by variation of the time element, dilution and acidity.

Blood Analysis. One c.c. samples of oxalated blood (always obtained with the patient in the fasting state) were dried and ashed using 0.5 gm. of calcium carbonate. One ashing was usually sufficient. Hydrolysis, oxidation and colorimetry were carried out as previously described. The final volume in each case was 100 c.c., 20 c.c. of which were used for the analysis.

Other chemical methods employed were as follows: Titratable acidity of urine, Henderson and Palmer[10]; ammonia in urine, Folin permutit colorimetric procedure[11a]; total nitrogen in urine, Folin micro Kjeldahl colorimetric procedure[11b]; creatinine in urine, Folin.[11c]

Results

In table 1 are presented the results of the balance studies carried out in four three-day periods during which no medication was given except for the daily administration of insulin and two Squibb's halibut liver oil capsules (plain). (These capsules were found on analysis to contain no iron.) As stated before, due to an error in collection, Period I included the feces of four days whereas Period II included those of two days. Hence the results for the first two periods have been averaged.

It is evident that the patient was in slightly positive iron balance throughout the time of study, retaining from 2.2 to 7.7 mg. of iron per three-day period or from 0.7 to 2.6 mg. per day (average, 1.8 mg. per day).

Following these basic observations, during five subsequent periods a study of the effect of acidosis upon the iron balance was attempted. Our purpose was to discover any possible influence of such an acidosis upon the mobilization of iron in the body. Unfortunately the results secured were largely invalidated by two factors: (1) Not enough time was available for developing a significant acidosis (ammonium chloride was used in gradually increasing dosage) and (2) when the ammonium chloride tablets were analyzed at the conclusion of the study, it was found that the "enteric" coating was rich in iron so that each 0.5 gram tablet furnished 8.27 mg. of iron. However, the results are not without interest and so are presented in table 2.

It will be noted that despite the mild acidosis, relatively large amounts of iron were retained in the body. Whether the somewhat lower values obtained during Periods VII, VIII and IX as compared with those during

TABLE I

Results of Studies of Iron Metabolism without Special Medication

Period	Dates (incl.) 1936	Blood Findings			Urinary Findings (other than iron)			Iron Metabolism (All values expressed per 3-day period)				
								Intake	Output			Balance
		Whole Blood Iron mg. per 100 c.c.	Hemoglobin per cent*	Erythrocytes per cu. mm.	NH_3 Nitrogen gm. per 24 hrs.	Total Nitrogen gm. per 24 hrs.	Creatinine gm. per 24 hrs.	Food: average value mg.	Urine mg.	Feces mg.	Total mg.	mg.
I	Oct. 30					10.6	0.91	50.7	1.1	55.6	Average = 44.5	+ 6.2
	Oct. 31											
	Nov. 1											
II	Nov. 2					10.8	0.96	50.7	1.6	30.7		
	Nov. 3											
	Nov. 4		88	4.44								
III	Nov. 5					10.4	0.91	50.7	1.1	41.9	43.0	+ 7.7
	Nov. 6											
	Nov. 7											
IV	Nov. 8	44				10.8	0.95	50.7	1.2	47.3	48.5	+ 2.2
	Nov. 9											
	Nov. 10		85	4.38	0.27							
Averages:	Per 3-day period							50.7	1.3	44.0	45.3	+ 5.4
	Per day							16.9	0.4	14.7	15.1	+ 1.8

* Newcomer glass standard; 100 per cent = 16.92 grams hemoglobin.

TABLE II

Results of Studies of Iron Metabolism During Administration of Ammonium Chloride *

Period	Date 1936	Blood Findings				24-hour Amount Urinary Findings (other than iron)				Iron Metabolism (All values expressed in mg. per 3-day period)						
										Intake			Output			
		Iron whole blood mg. per 100c.c.	Hemoglobin per cent	Erythrocytes millions per cu. mm.	Plasma CO_2 vols. per cent	Titratable Acidity c.c. normal acid	Ammonia Nitrogen gm.	Total Nitrogen gm.	Creatinine gm.	Food av. value	Ammonium Chloride	Total	Urine	Feces	Total	Balance mg.
V	Nov. 11	44				35.0	0.26	12.1	1.02	50.7	198.5	249.2	1.2	145.0	146.2	+103.0
	" 12					34.1	0.57									
	" 13	45			51	31.5	0.57									
VI	" 14					33.8	0.57	12.1	1.02	50.7	264.6	315.3	1.3	199.0	200.3	+115.0
	" 15					34.6	0.70									
	" 16	43			53	32.6	0.76									
VII	" 17					30.6	0.73	12.6	0.99	50.7	297.7	348.4	1.3	274.5†	275.8	+ 72.6
	" 18		82	4.14		43.9	1.05									
	" 19					37.8	1.11									
VIII	" 20				45	34.2	1.34	13.4	1.03	50.7	297.7	348.4	1.5	299.0	300.5	+ 47.9
	" 21					32.9	1.27									
	" 22	46				40.7	1.38									
IX‡	" 23				46	33.6	1.41	13.5	0.91	50.7	297.7	348.4	1.3	270.0	271.3	+ 77.1
	" 24	47	84	4.18		28.4	1.28									
	" 25				50											

* The ammonium chloride was administered in 0.5 gram tablets, the enteric coating of which was later found to contain on the average 8.27 mg. of iron per tablet.

† The feces were lost for one day of this period. The value obtained for the remaining 2 days, 183.0 mg., was multiplied by 3/2 to obtain 274.5 mg.

‡ This was a 2-day period. The values for iron intake and output have been multiplied throughout by 3/2.

Periods V and VI are significant, is difficult to say. It is interesting that throughout the entire study (see tables 1 and 2) the amount of iron excreted in the urine was quite constant, varying only from 1.1 to 1.6 mg. per three-day period.

Discussion

The most significant findings in the present report concern the iron balance in the 12 days during which the patient was on an ordinary liberal diabetic diet (containing a normal amount of iron) without medication of any type likely to influence iron metabolism. Under such conditions, with an intake of 16.9 mg. of iron each day, an average of 1.8 mg. was retained. This figure does not differ materially from that reported by others for normal individuals [12, 13, 14, 15] or for patients with hemochromatosis.[2, 3, 4, 5]

The small amount of iron retained daily is in keeping with the theory supported by Sheldon [16] and Dry and Wilder [17] to the effect that hemochromatosis is an "inborn error of metabolism" characterized by the slow and gradual, yet abnormal, accumulation of iron in the tissues over a period of years, probably a lifetime. Such an assumption seems necessary in order to reconcile this slow rate of deposition with the fact that the tissues of individuals dying with hemochromatosis contain large stores of iron. Thus Sheldon states that the total iron content of the body of such cases ranges from 25 to 50 gm. as compared with the normal of about 3 gm.[18] Taking the figure obtained with our patient as an example, one finds on calculation that if 1.8 mg. of iron is retained daily during a lifetime of 50 years, a total of slightly less than 33 grams would accumulate.

One other possibility is suggested by the results of Fowler and Barer.[5] In one of their patients regarded as having hemochromatosis in an early stage, a greater amount of iron was retained per day, 5.42 mg., than in three other cases of hemochromatosis or in two cases of diabetes mellitus without hemochromatosis. The possibility is suggested that in the earlier stages of the disease iron is retained in excessive amounts not demonstrable later. As Fowler and Barer themselves point out, however, their results can be taken only as suggestive since the patient was studied for only one six-day period. The interpretation of this finding must await confirmatory evidence.

In the second part of our own study in which ammonium chloride was given, it is noteworthy that neither the mild acidosis nor the increased intake of iron (supplied by the enteric coating of the tablets of ammonium chloride) caused any change in the output of iron in the urine. This value remained remarkably constant throughout the entire study. Our patient responded to an increased iron intake with an increased retention as has been true with subjects studied by others.[4, 5, 12, 13] Worthy of note is the fact that during the last three periods, less iron was retained than during the first two, suggesting that the limit of the body for retention had been approached. In making any interpretation, however, one must keep in mind the mild acidosis which existed.

‡ This was a 2-day period. The values for iron intake and output have been multiplied throughout by 3/2.

Some comment is needed regarding the values obtained for blood iron. They ranged from 43 to 47 mg. per 100 c.c. of whole blood and were thus well within the range found by Murphy, Lynch and Howard [19] in normal individuals. These workers found the average iron content of whole blood in normal young men to be 44.84 mg., in normal young women 42.48 mg., and in a group of 60 persons of both sexes and of varying age with an essentially normal blood (10 of the 60 had diabetes mellitus) 42.74 mg. per 100 c.c.

Summary

1. Studies are reported of the iron metabolism in a patient with hemochromatosis, a man aged 50.9 years with well-marked diabetes of 5.8 years' duration.

2. During four periods of three days each, it was found that with an average intake of 16.9 mg. of iron a day there was an average excretion of 0.4 mg. per day in the urine and 14.7 mg. per day in the feces, making a total output of 15.1 mg. per day and an average daily retention of 1.8 mg.

3. Studies designed to discover the effect of acidosis upon the mobilization of iron were inconclusive.

4. Values for the iron content of whole blood were within normal limits, ranging from 43 to 47 mg. per 100 c.c.

5. The findings are interpreted as supporting the theory that in hemochromatosis the abnormal retention of iron takes place slowly over many years of time, perhaps the lifetime of the individual. The possibility remains open, however, that in the earlier stages of the disease, retention of iron may take place at a more rapid rate than that evident in the patient studied.

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THE NATURE OF ARTERIAL HYPERTENSION WITH SPECIAL REFERENCE TO THE RÔLE OF THE KIDNEY *

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SINCE cardiac output,[1] blood volume,[2] and blood viscosity [3] are normal in patients with hypertension, the only remaining factor that might produce the elevated blood pressure is an increased peripheral resistance. This increased resistance is presumably generalized throughout the systemic circulation, and is the result of vascular hypertonus [4] confined to the arterioles although the small arteries may also be involved.[5]

The generalized arteriolar hypertonus responsible for hypertension could theoretically be produced by increased sympathetic vasomotor impulses or by circulating substances having a direct or indirect constrictor action on the arterioles.

Hypertension may be produced experimentally by means of renal ischemia,[7] ureteral obstruction,[8] removal of large amounts of kidney substance,[9] and by chemical,[10] serologic [11] and roentgenological [12] renal injuries. Complete unilateral or bilateral nephrectomy is not followed by hypertension.[13] It seems unlikely that a renal nervous mechanism is the cause since it has been found that denervation of the kidneys [14] or sympathectomy [15] does not prevent or relieve the hypertension induced by renal ischemia. Indeed, hypertension may be produced in dogs by ischemia of a kidney transplanted to the neck [16] or to the leg.[17] Goldblatt [18] has shown that clamping both renal arteries is followed by hypertension only if the renal veins are patent. This type of hypertension then is dependent upon a substance which is elaborated in the kidney and carried in the blood stream, and has a direct or indirect constrictor action on arterioles.

Since a pressor substance has been found to exist in normal kidneys [19] the theory that renal hypertension results from the humoral accumulation of this substance seems worthy of consideration. This view has been suggested in the past especially by Hartwich [20b] and Shaw [20a] but the evidence in favor of it has not been convincing.‡ It therefore seemed of interest to

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† Work done during the tenure of Richard and Ella Hunt Sutro Fellowships.

From the Medical Service of Dr. B. S. Oppenheimer and the Laboratory Division of The Mount Sinai Hospital, New York City.

‡ Hartwich [20b] ligated the renal artery and vein of one dog. The pressed juice of the necrotic kidney gave pressor effects but he was unable to determine whether or not this pressor effect was greater than that of the normal kidney of this animal or that of other kidneys of normal dogs. Hartwich did not measure the blood pressure of this animal but it is now known that ligation of the renal artery and vein is not followed by hypertension.[18]

learn whether extracts of kidneys taken from normal and from hypertensive animals differed in their content of pressor material.

Pressor Effects of Extracts of Kidneys From Hypertensive Dogs

Goldblatt and his co-workers [7] have shown that hypertension may be produced in dogs by constriction of one renal artery. A comparison, therefore, of the pressor effects of extracts made from the ischemic kidney with that of those prepared from the contralateral kidney from such an animal when hypertension has developed would appear to be of interest. Since the hypothetical agent would presumably be water soluble and since a water soluble renal pressor substance has been described, simple saline extracts seemed most suitable for the purpose.

Unilateral renal ischemia was produced in 30 dogs by means of the Goldblatt clamp. The blood pressure was measured by direct puncture of the femoral artery. A significant rise in blood pressure occurred in only 17, the average rise being 32 mm. mercury. The remaining animals were discarded. When the blood pressure, measured at frequent intervals after the operation, had risen significantly the animal was sacrificed by injecting chloroform intravenously. This generally took place in one to four days after constricting the renal artery. The operated and the unoperated kidneys were removed, weighed, and extracted separately.

The extracts were prepared in the following manner. All superfluous tissue was cut away and the capsule stripped off. The kidney was passed through a meat grinder, weighed and ground in a mortar for two minutes. One c.c. of physiological saline was added to each gram of tissue and the mixture ground for another two minutes and then placed in a mechanical shaker for a half hour. It was then centrifuged for 10 minutes and the supernatant fluid filtered.

The extracts of the ischemic and of the control kidney of the same animal were tested on cats and dogs anesthetized with nembutal and on unanesthetized dogs with van Leersum (carotid) loops. In the case of the anesthetized animals, 3 to 5 c.c. of the extracts to be tested were injected intravenously, and the effect upon carotid pressure noted. At least two animals were used for each set of comparisons.

In the case of the unanesthetized dogs, after a number of days of preliminary training, the animal was placed on its side for a 30 minute rest period. The systolic blood pressure was determined by palpation, two estimations being made every minute for a period of at least 15 minutes. The extract (5 to 7 c.c.) was then injected and further estimations of blood pressure made at similar intervals until the level, after rising, had begun to fall. The effect in millimeters of mercury was calculated as the difference between the mean of at least 30 readings before injection and the mean of an equal number obtained during a 15 minute period at the peak of the pressor response.

Injection of renal extracts into animals with or without anesthesia was usually followed by a transient fall and then a prolonged rise of blood pressure, returning gradually to the normal. Pressor effects were more constant, more pronounced and longer lasting in unanesthetized than in anesthetized animals, in some of the former being present for over two hours.

Results. In 16 out of 17 experiments the ischemic kidney had a greater pressor action than the control kidney of the same animal. In the remaining instance, no difference was noted. Depressor effects were produced by

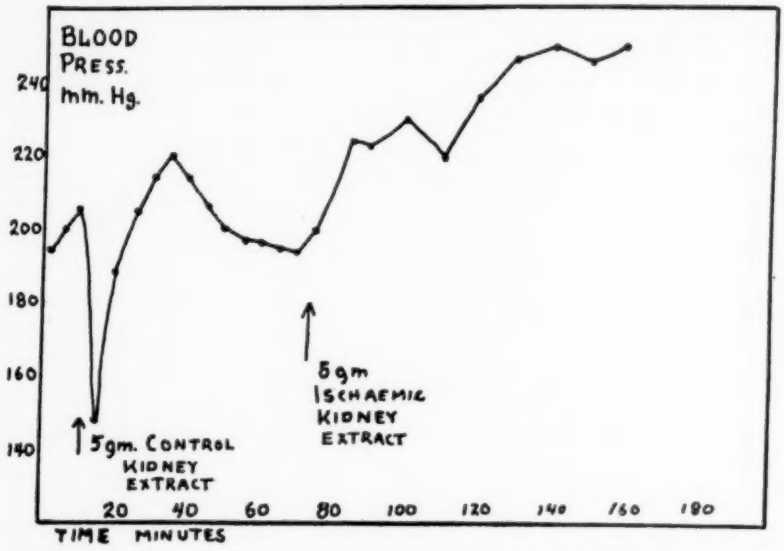

FIG. 1. Effect of intravenous injection of saline extracts of ischemic and unoperated kidney from dog with hypertension on blood pressure of unanesthetized dog with van Leersum loop.

11 of the control and only 2 of the ischemic kidney extracts. No rise in blood pressure occurred following the injection of 1 ischemic and 7 control kidney extracts (table 1, figure 1).

PRESSOR EFFECTS OF EXTRACTS OF ISCHEMIC SPLEEN AND MUSCLE

It is conceivable that the increased quantity of pressor substance found in ischemic kidneys might form in any tissue as a result of ischemia, and as such have no causal relation to hypertension. In order to test this possibility, similar observations were made on extracts of ischemic spleen and muscle. The splenic artery was constricted in four dogs and the femoral artery in two dogs by means of the Goldblatt clamp. After two to six days, saline extracts were made of the ischemic tissue and these were compared with extracts of normal spleen and muscle. In no instance did either the normal or ischemic spleen and muscle have a well defined pressor effect. Hypertension did not occur in any of the animals. This is in agreement with Goldblatt and his co-workers.[7]

TABLE I

Pressor Effects of Extracts of Ischemic and Unoperated Kidneys from Dogs with Hypertension Produced by Unilateral Renal Ischemia

Dog	Days After Operation	Test Animal	Effect of Ischemic Kidney Extract			Effect of Normal Kidney Extract			Difference in Pressor Effect Between Ischemic and Unoperated Kidney mm. Hg
			Depressor Effect mm. Hg	Pressor Effect		Depressor Effect mm. Hg	Pressor Effect		
				mm. Hg	Duration min.		mm. Hg	Duration min.	
1		Anesthetized dog	0	40	15+	20	15		25
2		Anesthetized dog	0	20	10	0	0		20
3		Anesthetized cat	0	40	20	40	0		40
57	4	Anesthetized cat	0	20	7	3	0		20
54		Anesthetized dog	20	35	8	20	20	5	15
78	13	Anesthetized cat	3	12	4	3	8	3	4
89	1	Anesthetized hypertensive dog	0	15		15	15		10
90	1	Anesthetized cat	0	0	0	0	0	0	0
97	3	Unanesthetized dog	0	58	120+	40	17	20	41
107	2	Unanesthetized dog	0	25	60	0	10	25	15
93	2	Anesthetized cat	0	40	60	0	15	3	25
111	1	Unanesthetized dog	0	27	50	0	21	60	6
115	3	Anesthetized cat	0	30	42	18	0		30
117	4	Anesthetized cat	0	36	90	0	25	3	11
128		Anesthetized dog	0	20		10	0	0	20
135		Anesthetized cat	0	20		35	0	0	20
130		Anesthetized dog	0	16		40	12		4

Discussion

These results demonstrate that saline extracts of ischemic kidneys from dogs, with experimental hypertension due to unilateral constriction of the renal artery, have greater pressor or lesser depressor effects than those of the opposite non-ischemic kidney. Since the hypertension in these animals must have a causal relationship to the ischemic and not the control kidney, it can then be concluded that the kidney which caused the hypertension possessed a greater quantity of pressor or lesser quantity of depressor substance. The greater pressor response elicited by the ischemic kidney extract was not due to a higher concentration of a normal amount of pressor material in a smaller mass since ischemic kidneys removed a short period after operation generally weighed more than the control specimens. Those removed at a later time often were smaller. Similar results have been independently obtained by Harrison, Blalock, and Mason [21] who produced hypertension in dogs by constricting the renal artery and by ureteral ligation.

In the present experiments the pressor substance from the ischemic kidneys was found to be more concentrated in the cortex than in the medulla, was destroyed by boiling for five minutes, and did not dialyze through a semipermeable membrane. Since similar properties have been attributed to extracts of normal kidneys,[19] the substance present in increased amounts in ischemic kidneys is probably similar to that first described by Tigerstedt and Bergman.[19a] The absence of increased pressor activity in ischemic spleen, renal medulla, and striated muscle suggests that this is not a nonspecific property but is apparently peculiar to kidney cortex.

Pressor Effects of Extracts of Human Kidneys

In view of the findings in dogs, it seemed of importance to determine the pressor effects of extracts of kidneys from human beings with normal and elevated blood pressures. Kidneys were obtained after death from 21 subjects who had had hypertension of various types during life. Of these 12 were diagnosed as benign hypertension, five as malignant hypertension, two as chronic glomerulonephritis, and two showed pyelonephritic contracted kidneys with hypertension. The kidneys of 24 individuals of approximately the same age group, who had normal blood pressure during life and who had normal kidneys at autopsy, were extracted as controls. The organs were obtained at varying intervals after death. The extracts were prepared in the manner previously described. In these experiments it was necessary to test the pressor properties of extracts obtained over a period of several months under uniform circumstances on a test object which would remain as constant as possible over this period of time. Forty-one of the 45 extracts were tested in the manner described above on two trained unanesthetized dogs, with van Leersum (carotid) loops. Approximately the same number of extracts prepared from kidneys of normal and hypertensives were injected into each dog. The remaining four extracts,

of which two were from normal and two from hypertensive individuals, were tested on anesthetized animals. The equivalent of 7 grams of tissue was injected into the unanesthetized and 3 to 5 grams into the anesthetized animals.

Results. The average pressor effect of the 21 extracts from the kidneys of hypertensive patients was 26 mm. mercury (standard deviation of the mean—3.4 mm. mercury), with a range between 9 and 60 mm. mercury. The mean pressor effect of the 24 extracts in the non-hypertensive group was 14 mm. mercury (standard deviation of the mean 2.7 mm. mercury), the range being from 0 to 48 mm. mercury. No significant difference was noted in the depressor effects of the two groups (tables 2 and 3, figure 2).

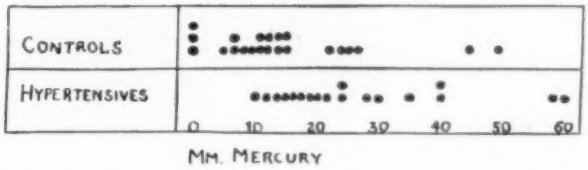

FIG. 2. Pressor effect in millimeters of mercury of saline extracts of kidneys from human beings.

The mean pressor effect of the 17 extracts from kidneys of patients with so-called essential hypertension (benign and malignant) was 23.8 mm. mercury (the standard deviation being 3.4 mm. mercury).

DISCUSSION

It may be seen that considerable variation exists in both series, the extracts of some kidneys from patients who had marked hypertension during life producing only slight pressor actions, whereas others in the control group had marked effects.

It is possible that the variations observed may be in part at least due to complicating factors such as postmortem changes and manner of death. It was frequently impossible to obtain accurate weights of the kidneys and the patients. It is probable that in relation to body weight, the weights of the hypertensive kidneys were smaller than the control kidneys; and since the same amount of renal tissue was used in the case of both extracts, it is likely that in some instances the pressor material might have been present in normal amount but at the same time in greater concentration in the smaller hypertensive kidneys. The exclusion of the four severely contracted kidneys which were the only instances of so-called renal hypertension did not significantly alter the results. More work with purer, fresher extracts from kidneys of known weights must be done before final conclusions can be drawn.

It is not known whether the pathogenesis of human hypertension is the same as in experimental hypertension due to renal ischemia. The high

TABLE II

Vasomotor Effects of Kidney Extracts from Human Beings with Hypertension

Case	Age	Sex	Blood Pressure	Diagnosis	Cause of Death	Kidney Function	Condition of Kidneys	Time Tested After Death*	How Tested	Result mm. Mercury		Duration of Pressor Effect in Minutes
										Depressor Effect	Pressor Effect	
1	58	F	190/100	Benign hypertension	Heart failure	Normal	Congested. Benign nephrosclerosis	24 hrs.	Anesthetized dog Anesthetized cat	25 10	15 16	15 45
2	30	M	190/100	Benign hypertension	Bronchopneumonia	Normal	Benign nephrosclerosis	24 hrs.	Anesthetized dog Anesthetized cat	0 0	10 9	
3	45	F	280/160	Malignant hypertension	Bronchopneumonia	Moderately impaired	Malignant nephrosclerosis	24 hrs.	Unanesthetized dog	50	40	Over 160
4	39	M	160/100	Chronic glomerulonephritis	Uremia	Severely impaired	Chronic glomerulonephritis. Pyelitis	48 hrs.	Unanesthetized dog with van Leersum loop	100	28	80
5	52	M	190/110	Benign hypertension	Bronchopneumonia	Normal	Benign nephrosclerosis	48 hrs.	Unanesthetized dog with van Leersum loop	80	40	Over 160
6	?	F	210/110	Pyelonephritis	Heart failure	Moderately impaired	Pyelonephritic contracted kidneys	24 hrs.	Unanesthetized dog with van Leersum loop	50	35	170
7	67	F	260/110	Benign hypertension	Cerebrovascular accident	Moderately impaired	Benign nephrosclerosis. Congestion	48 hrs.	Unanesthetized dog with van Leersum loop	60	58	Over 90
8	65	F	190/100	Benign hypertension	Heart failure	Normal	Benign nephrosclerosis. Congestion	48 hrs.	Unanesthetized dog with van Leersum loop	5	24	Over 60
9	63	F	190/100	Benign hypertension	Carcinoma of stomach	Normal	Benign nephrosclerosis	12 hrs.	Unanesthetized dog with van Leersum loop	0	19	80
10	64	M	210/110	Benign hypertension	Carcinoma of pancreas	Normal	Benign nephrosclerosis. Bile-stained	52 hrs.	Unanesthetized dog with van Leersum loop	55	22	100

* These figures are accurate within 12 hours.

TABLE II—*Continued*

* These figures are accurate within 12 hours.

TABLE II—*Continued*

Case	Age	Sex	Blood Pressure	Diagnosis	Cause of Death	Kidney Function	Condition of Kidneys	Time Tested After Death*	How Tested	Result mm. Mercury		Duration of Pressor Effect in Minutes
										Depressor Effect	Pressor Effect	
11	28	F	190/110	Chronic glomerulonephritis	Uremia	Severely impaired	Chronic glomerulonephritis	48 hrs.	Unanesthetized dog with van Leersum loop	40	24	60
12	30	M	250/152	Malignant hypertension	Uremia	Severely impaired	Malignant nephrosclerosis	50 hrs.	Unanesthetized dog with van Leersum loop	50	17	Over 90
13	69	F	240/150	Benign hypertension	Cerebral thrombosis	Normal	Benign nephrosclerosis	48 hrs.	Unanesthetized dog with van Leersum loop	60	12	Over 60
14	67	M	240/132	Benign hypertension	Cerebral hemorrhage		Benign nephrosclerosis	24 hrs.	Unanesthetized dog with van Leersum loop	25	13	Over 80
15	43	F	240/150	Pyelonephritis hypertension	Uremia. Congestive failure	Severely impaired	Pyelonephritic contracted kidneys	4 hrs.	Unanesthetized dog with van Leersum loop	0	60	Over 170
16	44	F	280/190	Malignant hypertension	Uremia	Moderately impaired	Malignant nephrosclerosis	90 hrs.	Unanesthetized dog with van Leersum loop	30	16	20
17	52	M	260/160	Malignant hypertension	Uremia	Severely impaired	Malignant nephrosclerosis		Unanesthetized dog with van Leersum loop	0	20	50
18	51	F	180/95	Benign hypertension	Coronary thrombosis	Normal	Benign nephrosclerosis		Unanesthetized dog with van Leersum loop	70	30	Over 65
19	23	F	150/120	Libman-Sachs disease	Uremia	Impaired	Intracapillary glomerulonephritis	8 hrs.	Unanesthetized dog with van Leersum loop	0	13	40
20	52	M	160/90	Benign hypertension	Cerebral hemorrhage	Normal	Benign nephrosclerosis	24 hrs.	Unanesthetized dog with van Leersum loop	20	14	30
21	45	F	240/130	Benign hypertension	Uremia. Thrombosis of splenic artery	Impaired	Benign nephrosclerosis	24 hrs.	Unanesthetized dog with van Leersum loop	0	38	Over 50

* These figures are accurate within 12 hours.

TABLE III

Vasomotor Effects of Kidney Extracts from Human Beings with Normal Blood Pressure

Case	Age	Sex	Blood Pressure	Cause of Death	Condition of Kidneys	Time Tested After Death*	How Tested	Results mm. Mercury		Duration of Pressor Effect
								Depressor Effect	Pressor Effect	
1	47	M	110/72	Coronary occlusion	Normal	24 hrs.	Anesthetized dog	60	0	
							Anesthetized cat	25	0	
2	30?	M		Bullet wound	Normal	12 hrs.	Anesthetized dog	40	10	5 minutes
							Anesthetized cat	35	0	
3	50?	M	120/70	Pulmonary embolism	Normal	48 hrs.	Unanesthetized dog van Leersum loop	80	26	50 minutes
4	28	F		Subdural hematoma (traumatic)	Normal	48 hrs.	Unanesthetized dog van Leersum loop	30	12	40 minutes
5	36	M	120/80	Pulmonary embolism	Normal	24 hrs.	Unanesthetized dog van Leersum loop	20	11	90 minutes
6	66	M	120/70	Cirrhosis of liver. Mesenteric thrombosis	Normal	48 hrs.	Unanesthetized dog van Leersum loop	0	48	Over 120 minutes
7	65	M	90/60	Peritonitis. Bronchopneumonia	Congested	12 hrs.	Unanesthetized dog van Leersum loop	5	0	
8	65	M	90/60	Shock. Luetic aortitis	Slight pyelitis	24 hrs.	Unanesthetized dog van Leersum loop	50	8	Over 60 minutes
9	62	M	90/60	Pneumonia	Normal	24 hrs.	Unanesthetized dog van Leersum loop	70	15	40 minutes
10	54	M	120/70	Hemorrhage into peritoneal cavity. Cirrhosis of liver	Normal	48 hrs.	Unanesthetized dog van Leersum loop	0	12	Over 65 minutes
11	51	F	120/60	Mesenteric thrombosis	Normal	12 hrs.	Unanesthetized dog van Leersum loop	0	25	Over 70 minutes
12	13	F	100/60	Peritonitis	Normal	12 hrs.	Unanesthetized dog van Leersum loop	40	7	40 minutes

* These figures are accurate within 12 hours.

TABLE III—*Continued*

Case	Age	Sex	Blood Pressure	Cause of Death	Condition of Kidneys	Time Tested After Death*	How Tested	Results mm. Mercury		Duration of Pressor Effect
								Depressor Effect	Pressor Effect	
13	62	M		Lobar pneumonia	Parenchymatous degeneration	12 hrs.	Unanesthetized dog van Leersum loop	0	10	Over 80 minutes
14	48	F		Pericarditis	Normal	12 hrs.	Unanesthetized dog van Leersum loop	15	12	60 minutes
15	9	F	80/60	Bronchopneumonia	Normal	12 hrs.	Unanesthetized dog van Leersum loop	25	0	
16	38	F	80/60	Carcinoma of ovary	Normal	12 hrs.	Unanesthetized dog van Leersum loop	0	11	60 minutes
17	52	M	120/80	Carcinoma of pancreas	Normal	24 hrs.	Unanesthetized dog van Leersum loop	25	15	Over 60 minutes
18	26	M	96/68	Thrombophlebitis with abscesses	Normal	24 hrs.	Unanesthetized dog van Leersum loop	0	22	Over 60 minutes
19	42	F	130/80	Carcinoma of pancreas	Normal	10 hrs.	Unanesthetized dog van Leersum loop	25	0	
20	55	M	120/70	Pneumonia. Otitis media	Normal	24 hrs.	Unanesthetized dog van Leersum loop	0	44	60 minutes
21	14	M	120/80	Septicemia	Normal	18 hrs.	Unanesthetized dog van Leersum loop	15	24	Over 45 minutes
22	38	F	140/86	Asthma	Normal	24 hrs.	Unanesthetized dog van Leersum loop	20	7	20 minutes
23	42	M	120/60	Peritonitis. *B. welchii* infection	Normal	15 hrs.	Unanesthetized dog van Leersum loop	0	14	
24	68	M	126/80	Carcinoma of esophagus with metastases	Normal	8 hrs.	Unanesthetized dog van Leersum loop	25	0	

* These figures are accurate within 12 hours.

incidence of arteriolar lesions in the kidney,[22] the persistence of vascular hypertonus following removal of vasoconstrictor tone,[23] and the occasional cure of hypertension following removal of a pathological kidney [24] suggest that hypertension in human beings results from a similar mechanism.

The demonstration of an increased amount of pressor substance in kidneys of hypertensives does not necessarily prove that this substance is the cause of the elevation in blood pressure. However, it is compatible with the hypothesis that hypertension is the result of an increased humoral accumulation of a pressor substance normally elaborated by the kidneys. The failure of hypertension to develop following renal ischemia in adrenalectomized animals and the protective effect of non-ischemic renal tissue indicate that other factors are concerned. Final proof would seem to reside in the finding of an increased quantity of this substance in the blood of hypertensive subjects.

Conclusions

1. Hypertension was produced in 17 dogs by means of unilateral renal ischemia.

2. Saline extracts of the ischemic kidney produced greater pressor effects than extracts of the contralateral control kidney in 16 of the 17 experiments. Saline extracts of ischemic kidney also produced lesser depressor effects than extracts of the control kidneys.

3. Saline extracts of ischemic spleen and muscle did not have any pressor actions.

4. The mean pressor effect of saline extracts of kidneys from 21 patients who had hypertension of various types during life was greater than that of renal extracts from 24 subjects who had had normal blood pressures.

5. These observations are compatible with but do not prove the hypothesis that hypertension in man (both "essential" and "renal") and in animals is due to an increased humoral accumulation of a pressor substance normally elaborated by the kidney.

The authors want to thank Drs. B. S. Oppenheimer and Harry Goldblatt for aid and advice.

Since the completion of this work Pickering and one of the authors of this paper (M. P.) have determined the quantity of renin in hypertensive rabbits. Employing the method of assay and extraction recently described (Pickering, G. W., and Prinzmetal, M.: Some observations on renin, a pressor substance contained in normal kidney together with a method for its biological assay, Clin. Sci., 1938, iii, 211), no significant increase in the amount of renin was found in kidneys of hypertensive rabbits.

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VASOMOTOR EFFECTS OF BLOOD IN PATIENTS WITH HYPERTENSION AND ANIMALS WITH EXPERIMENTAL HYPERTENSION *

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RECENT investigations have suggested that the abnormal vasoconstriction in animals and patients with persistent hypertension is due to a nonnervous and presumably chemical mechanism.[1, 2, 3, 4, 5] Increased amounts of a pressor substance have been demonstrated in saline extracts made from kidneys of dogs with renal hypertension and from kidneys of patients suffering from hypertensive disease.[6, 7] These observations are compatible with the hypothesis that such forms of hypertension are due to the humoral accumulation of a pressor substance of renal origin. This hypothesis would be verified by the demonstration of increased amounts of the substance in the blood stream in patients or animals with hypertension. Many workers have sought such circulating pressor materials. The literature has been adequately reviewed in several recent reports.[8, 9, 10] In general the results have been conflicting even when identical methods were employed. In view of these considerations it seemed important to look anew in the circulating blood stream.

The following experiments were carried out:

1. Cross transfusion between patients with hypertension and subjects with normal cardiovascular systems.
2. Comparison of the vasomotor effects of the plasma from patients with elevated and those with normal blood pressures by perfusion of the rabbit's ear preparation.
3. Comparison of vasoactive properties of blood taken from normal and hypertensive dogs by perfusion through tissues of dogs with experimental hypertension.
4. Study of the vasomotor activity of renal vein blood obtained from animals rendered hypertensive by means of renal ischemia.

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Preliminary reports of this paper have appeared:

FRIEDMAN, B., and PRINZMETAL, M.: Vasomotor effects of blood in hypertension, Proc. Soc. Exper. Biol. and Med., 1936, xxxiv, 543.

PRINZMETAL, M., FRIEDMAN, B., and ROSENTHAL, N.: Nature of peripheral resistance in arterial hypertension, *Ibid.*, 1936, xxxiv, 546.

† Work done during the tenure of Richard and Ella Hunt Sutro Fellowships.
From the Medical Service of Dr. B. S. Oppenheimer at Mount Sinai Hospital, New York City.

Cross Transfusion of Blood between Subjects with Hypertension and Patients with Normal Blood Pressure

Høst [11] and Pickering [12] observed no elevation in blood pressure in the recipient following transfusion of as much as 700 c.c. of blood from donors with hypertension. Collins and Hoffbauer [13] likewise observed no pressor effect in normal dogs receiving large quantities of blood from dogs with experimental renal hypertension. In the following observation an interchange of large amounts of whole blood between patients with malignant hypertension and subjects with normal cardiovascular systems was effected by the method of cross transfusion. This experiment was done not only because of its theoretical implications but also because of its possible therapeutic value. If hypertension is due to the increased concentration of a pressor substance in the blood stream one would expect the hypertensive patient to have a fall in blood pressure consequent on dilution by the normal blood. Likewise, the individual with normal blood pressure should have an elevation of blood pressure because of the increased concentration of pressor material in the transfused blood of the hypertensive donor.*

The subjects, of the same blood group, were kept in bed and the blood pressure determined daily for a period of one week. They were then placed head to head with the arms extended. Two Unger transfusion sets were used, both operated at the same speed so that a gradual mixture of the blood of the two patients was brought about without a change in blood volume in either one. This technic does not require anti-coagulants and lasts about 30 minutes. During the transfusions repeated auscultatory blood pressure determinations were made at the popliteal arteries of both subjects. Four such procedures were carried out, the amounts of blood exchanged being 500, 650, 1460, and 2000 c.c. In these experiments a certain amount of blood was necessarily transferred back to the original subject, especially during the later stage of the procedure. In order to find the ratio of transfused blood to the computed total circulating blood volume, Congo red was injected intravenously into the individual with normal blood pressure immediately before the transfusion of 2000 c.c. of blood. At the end of the transfusion 42 per cent of the total circulating dye of both subjects was found in the hypertensive individual. With this information and knowing the total blood volume of each subject, the ratio of transfused blood to total circulating blood volume was computed for each person.

In no instance was there a significant change in blood pressure in either the hypertensive or normal subject during or for a period of one week following the transfusion. (Figures 1A and 1B.)

It is possible that the failure to demonstrate a pressor substance in the blood of patients with malignant hypertension is due to its dilution by the tissue fluids of the recipient. It is also possible that malignant hypertension is not renal in origin and that an increased concentration of pressor substance occurs only in "renal" hypertension. Evidence has been obtained,

*The subjects with normal cardiovascular systems had inoperable carcinomata.

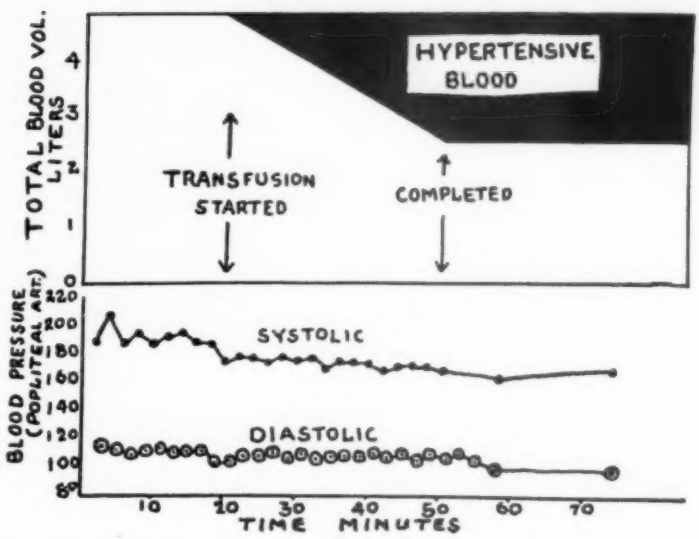


FIG. 1 *A*. Popliteal blood pressure of patient with carcinoma of the larynx and normal cardiovascular system receiving 2000 c.c. of blood from donor with malignant hypertension during cross-transfusion.

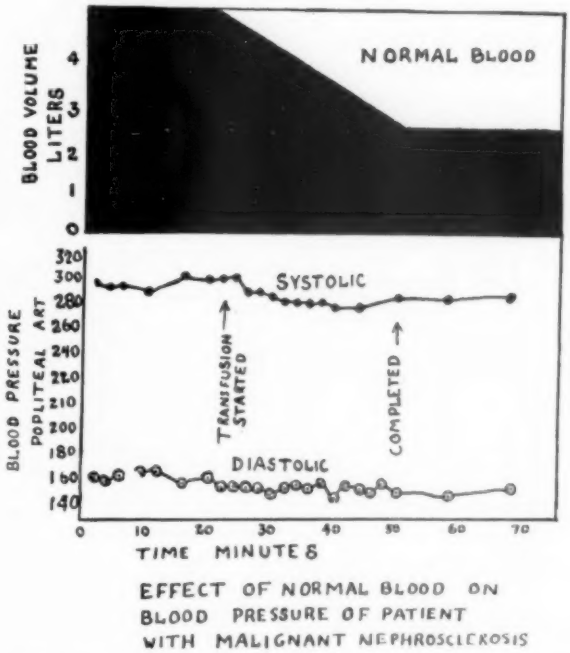


FIG. 1 *B*. Popliteal blood pressure of patient with malignant hypertension receiving 2000 c.c. of blood from donor with normal blood pressure during cross-transfusion.

however, that increased amounts of pressor substance may be present in the kidneys of subjects who had had "essential" hypertension (benign and malignant) during life.[14] Other methods were used which might overcome these difficulties.*

Determination of Vasomotor Effects of Blood of Patients with Hypertension by Perfusion of the Rabbit's Ear

The rabbit's ear preparation is very sensitive to known vasoactive substances and has been used as a test object by several workers, all of whom obtained pressor effects with blood from subjects with various types of hypertension. Kahlson and von Werz [16] found pressor substances in the blood of old patients with hypertension and also in patients suffering from febrile diseases. Kuri, Nakaya, Murakami and Okinaka,[17] using arterial blood with precautions to prevent oxidation, observed increased vasoconstrictor activity in patients with hypertension. They believed the vasoactive material to be epinephrine. Brand and Katz [18] detected pressor substances in patients with paroxysmal hypertension during the crises. The vasoconstrictor effect, like that of epinephrine, was prevented by ergotoxine. Volhard [19] reports the observations of Bohn who noted pressor properties in extracts prepared from the blood of patients with renal (pale) hypertension but not in those with "red" hypertension. Hantschman [20] on the other hand reported vasoconstrictor activity in all types of hypertension as well as in the blood of animals with experimental renal injuries.

To detect the presence of a hypothetical pressor substance it would seem most desirable to use blood with minimum of change and a test object with maximum sensitivity to known pressor substances. Concentration or extraction of the material although desirable cannot logically be performed until the chemical properties of the substance are known. For this reason whole undiluted blood plasma was used and perfused through the isolated rabbit's ear.

The method first described by Krakow and Pissemski [21] consists of perfusion through the central artery of the amputated rabbit's ear attached to a long vertical glass tube which acts as a pressure gauge. Fluid is allowed to drip in at the top of the tube at a constant rate and forms a level in the tube. A change in the resistance of the vascular bed will be reflected by a change in the level of the fluid in the tube if the inflow remains constant. A Mariotte bottle did not give uniform inflow. For this purpose a constant volume pump [22] was found to be satisfactory.

Blood was collected from the antecubital veins of subjects with normal and elevated blood pressures, centrifuged, filtered, and used immediately. Heparin or citrate served as an anticoagulant. We have found that by this method one may detect

* It was suggested that the failure of the blood pressure to rise in the normal subject might be due to the increased renal excretion of the hypothetical pressor substance by the normal kidney. For this reason, in one experiment, the urine of the individual with normal blood pressure was collected for 24 hours before and immediately following transfusion. Extracts were prepared and vasomotor effects compared according to the method of Capps and his co-workers.[15] No difference was noted between the extracts made from the urine excreted before and that immediately following the transfusion.

epinephrine in concentration of 1 to 100,000,000 and pituitrin in 1 to 150,000. The surface tension and viscosity of the plasma were measured since it is well known that these properties may affect the rate of flow. The ear was perfused first with Tyrode's solution until the tonus of the vessels became constant (50 to 60 minutes). Plasma was then introduced, alternating back and forth between that taken from the hypertensive and control patient. A few drops of Congo red added to one of the samples facilitated its detection as it entered the ear. Before terminating the experiment varying concentrations of pitressin, ephedrine, epinephrine, or guanidine were added to the plasma to test the reactivity of the preparation.

The vasomotor effect of the blood from 20 patients with various types of hypertension was compared with that of 20 patients with normal blood pressure. The former group consisted of eight subjects with benign hypertension, two with malignant hypertension, seven in various stages of glomerulonephritis, one with polycystic kidney disease, and two with hypertension associated with Cushing's syndrome. The plasma of three patients with acute glomerulonephritis was tested during the active phase of the disease when hypertension was present and following recovery when the blood pressure declined to the normal level, each case thus serving as its own control.

TABLE I

Vasomotor Effects of Blood from Patients with Hypertension as Compared with That of Subjects with Normal Blood Pressure Tested by Means of Perfusion of Rabbit's Ear

Type of Hypertension	Response with Respect to Normal			
	Pressor	Unchanged	Depressor	Total
Benign	1	4	3	8
Malignant	0	0	2	2
Glomerulonephritis				
Acute	1	0	3	4
Subacute or chronic	0	1	2	3
Polycystic kidney disease	0	0	1	1
Cushing's syndrome	0	0	2	2
	2	5	13	20

Results (Table 1). In 13 instances the plasma of the hypertensive subjects was depressor, in 2 cases pressor, and in 5 instances no differences were observed as compared with the plasma of normal individuals. In all three subjects with acute glomerulonephritis, the blood was depressor during the hypertensive phase of the disease. Following recovery, the depressor effect persisted in one instance, while in the other two the plasma became pressor with respect to that of control subjects. Figures 2*A* and *B* illustrate the findings in one experiment.

The changes could not be attributed to variations in viscosity or surface tension since these properties varied only slightly and in no consistent direction. Following the addition of minute amounts of known pressor sub-

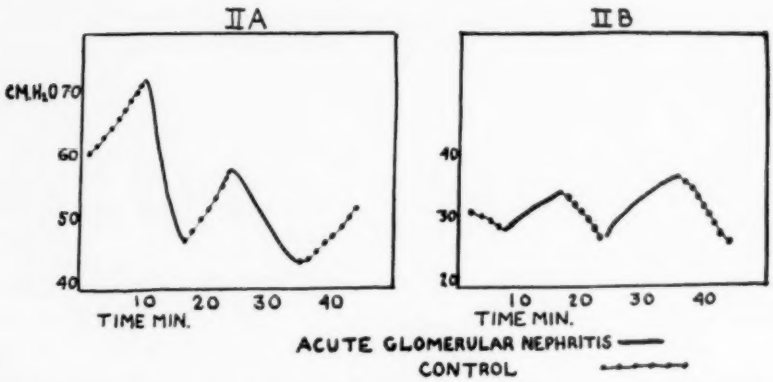


FIG. 2 *A* and *B*. Vasomotor effect on the rabbit's ear of plasma of patient with acute glomerulonephritis compared with that of a normal subject.

A. April 13, 1936. Depressor effect during hypertensive phase. Blood pressure 160/110.

B. April 23, 1936. Pressor effect in recovery phase. Blood pressure 130/80.

stances (epinephrine 1 to 100,000,000) the plasma from both hypertensive and control patients invariably developed vasoconstrictor properties.

VASOMOTOR EFFECTS OF PLASMA FROM A SUBJECT WITH HYPERTENSION DUE TO ADRENAL PHEOCHROMOCYTOMA

It is well known that certain tumors of the adrenal medulla are associated with hypertension of a paroxysmal nature. Since epinephrine has been found in the tumors,[23] it has been assumed that the hypertension in patients with pheochromocytomata is due to hyperepinephremia. This type of hypertension would seem to be physiologically similar to that induced by the administration of epinephrine. A study of the vasomotor properties of the blood of such patients using the perfusion method previously described is of theoretical and some practical interest, since with this method no pressor substance has been detected in the blood of subjects with the ordinary types of hypertension. We have had the opportunity to study such a patient.*

A 26-year-old woman for a period of 7 years had had recurrent attacks characterized by hypertension (300 plus systolic, 160 to 200 diastolic); tachycardia; throbbing headache; palpitation; choking sensations; numbness and blanching of the fingers, toes, and tip of the nose; profuse perspiration and tenseness. The attacks could be precipitated by exertion and lasted from 5 to 15 minutes. Between attacks the blood pressure level was slightly elevated (160/120). At operation a large adrenal tumor was found and removed. The tumor showed the typical histological appearance of a pheochromocytoma, and epinephrine-like substances were extracted and demonstrated by chemical and physiologic tests. Following operation the attacks disappeared and the blood pressure fell gradually over a period of several days to a

* This case has been reported in full elsewhere:

BEER, E., KING, F. H., and PRINZMETAL, M: Pheochromocytoma with demonstration of pressor (adrenalin) substance in the blood preoperatively during hypertensive crisis, Ann. Surg., 1937, cvi, 85.

level of 130/90 where it has remained. The patient has been symptom-free for a period of 12 months. (October 1937.)

The vasomotor effect of plasma collected during an attack of hypertension (blood pressure 300 plus systolic, 200 diastolic mm. mercury) was tested. Following operation when the blood pressure had fallen to 130/90 the plasma was again tested. During the attack of hypertension, the plasma had a very marked pressor effect compared with that of a control subject.

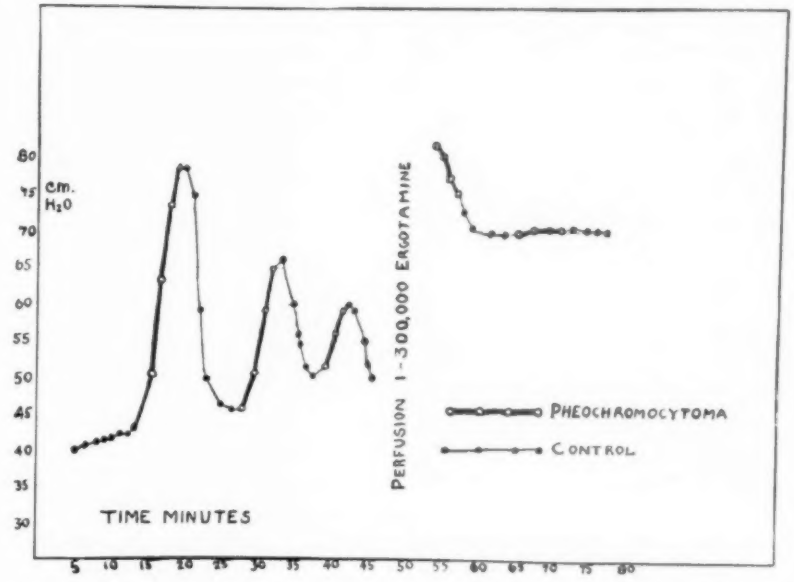
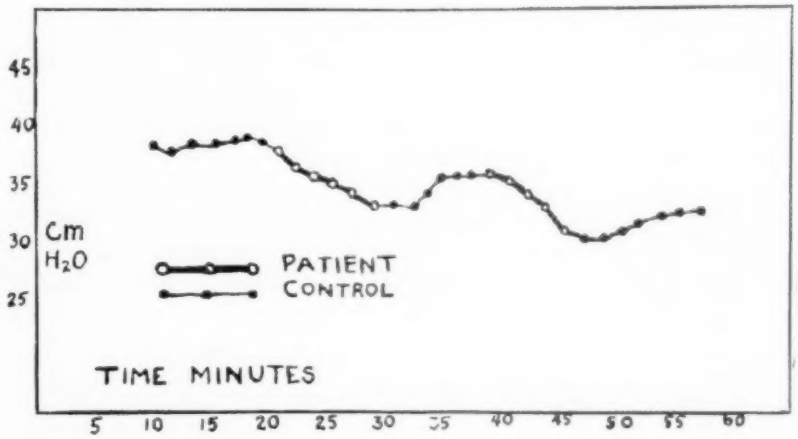


FIG. 3 *A* and *B*. Vasomotor effect on the rabbit's ear of plasma of patient with hypertension due to pheochromocytoma as compared with that of a control subject.

A. During a paroxysm of hypertension (blood pressure 300 plus/200) before operation showing pressor effect abolished by ergotamine.



B. After operation blood pressure 130/90 showing relative depressor effect.

This pressor effect was prevented when the rabbit's ear had been previously perfused with ergotamine tartrate (1:400,000). Following operation, when the blood pressure was normal, the pressor effect of the blood had entirely disappeared (figure 3).

Discussion. The results demonstrate that the method is capable of detecting the presence of circulating epinephrine in concentrations sufficient to cause hypertension. It further serves to differentiate this rare type of hypertension from the ordinary types previously described.

The failure to detect such substances in the blood of patients with ordinary types of hypertension is evidence against the hypothesis that an increased concentration of circulating epinephrine-like substances is responsible for the elevation in blood pressure in these cases.

The Perfusion of Tissues of Hypertensive Dogs with Blood from Normal and Hypertensive Dogs

The methods previously employed in testing for a pressor substance involved the use of tissues of normal animals as test objects. It seemed possible that such a substance might act only on vessels of animals with hypertension. For this reason other experiments were performed in which the tissues of hypertensive dogs were used as test objects. Furthermore, in these experiments the blood and test object were taken from animals of the same species.

The Perfusion of Hypertensive Dogs' Tails. Hypertension was produced in dogs by constricting both renal arteries.[24] After the blood pressure had risen, the animals were heparinized, bled from the carotid artery and their tails amputated. The central artery of the tail was then cannulated and perfused by means of a constant volume pump with whole heparinized blood heated to body temperature. The pressure required to force a given volume of blood through the tail was recorded. The initial level of perfusing pressure was adjusted to approximate the level of the mean blood pressure of the dog prior to bleeding. The vasomotor effects of the animal's own (hypertensive) blood were compared with those taken from normal dogs. If hypertension were due to an increased concentration of a pressor substance, normal blood should result in dilatation of the hypertonic vessels.

The experiment was performed five times. In three instances the blood taken from the hypertensive dog was depressor, in one case pressor as compared with normal blood, and in the remaining instance no difference was observed. The addition of minute amounts of epinephrine to the hypertensive animals' blood in four experiments caused it to become pressor when it was not originally so.

Perfusion of Hypertensive Dogs' Legs. These experiments were carried out by the technic of retrograde perfusion described by Cattel[25] and modified by Harrison and Burch.[26] The method permits perfusion of tis-

sues at any desired pressure at the same time insuring an adequate blood supply between periods of perfusion.

A cannula with opening directed centrally was placed in the femoral artery distal to the branching of the profunda femoris. The cannula was connected to a heating coil warmed to body temperature and to a graduated burette in which the pressure was regulated by a pressure bottle. During periods of perfusion a clamp was placed on the femoral artery proximal to the profunda branch, the blood flowing from the burette through the heating coil and cannula up the femoral artery and into the profunda and other branches of the femoral artery between the clamp and cannula. Between periods of perfusion the clamp was applied to the femoral artery just central to the cannula, thus reëstablishing the normal circulation to the tissues under observation.

The hypertensive animal's own blood and oxygenated heparinized blood from a normal dog were perfused alternately under a constant pressure equal to the mean pressure of the dog in the femoral artery of the unoperated leg. The time required for 50 c.c. of blood to flow into the leg was measured. Four such procedures were carried out. The results are summarized in table 2. In two experiments the blood from the normal animals

TABLE II

Vasomotor Effects of Blood from Dogs with and without Hypertension Tested on Legs of Hypertensive Dogs by Means of Retrograde Perfusion

Exper. No.	Time of Flow for 50 c.c.		Time of Flow for 50 c.c.	
	Blood from Normal Dog	Number of Trials	Blood from Hypertensive Dog	Number of Trials
I	52 sec.	3	59 sec.	4
II	57 sec.	4	47 sec.	9
III	30 sec.	3	32 sec.	3
IV	46 sec.	3	42 sec.	3

flowed somewhat faster (i.e. was vasodilator) with respect to that taken from hypertensive animals. Opposite results were obtained in the other two instances. In two experiments comparisons of vasoactive properties of the blood were made on the dog's leg after severance of the nerve connections by means of a guillotine incision at the upper thigh, involving all the tissues of the leg except for the femoral artery and vein and the femur. This procedure did not alter the results.

Neither in this nor in the preceding experiment was there any consistently greater pressor activity in the blood of animals with hypertension when perfused through its own tissues as compared with blood from normal animals.

PRESSOR EFFECTS OF RENAL VEIN BLOOD

If a pressor substance of renal origin is responsible for the elevation of blood pressure in renal hypertension it should be present in highest concentrations in the renal vein blood. For this reason it would appear advisable

to compare the vasomotor properties of renal vein blood coming from ischemic and from normal kidneys.

Hypertension was produced in eight dogs by constricting one renal artery. After the blood pressure had risen significantly (average 32 mm. of mercury) the animals were heparinized and under nembutal anesthesia an abdominal incision was made and both renal veins cannulated. Blood from the normal and ischemic kidney was collected simultaneously, centrifuged, filtered, and the vasomotor effects of the plasma compared. The dog's tail amputated at the completion of the collection of the blood samples was used as a test object, the method being the same as that previously described for the rabbit's ear.

The blood coming from the ischemic kidney was depressor in five cases and pressor in three instances as compared with blood from the unoperated kidney of the same animal (table 3). These results agree with those of

TABLE III

Vasomotor Effects of Renal Vein Blood from the Ischemic and Unoperated Kidney of Dogs with Hypertension Due to Unilateral Renal Ischemia

Exp. No.	Elevation of Blood Pressure Following Renal Ischemia mm. mercury	Test Object	Relative Effect of the Blood from Ischemic Kidney
1	35	Hypertensive Dog's Tail	Depressor
2	45	"	Pressor
3	30	"	Depressor
4	35	"	Depressor
5	40	"	Pressor
6	35	"	Pressor
7	10	"	Depressor
8	25	Rabbit's Ear	Depressor

Collins and Hoffbauer who found no increased pressor effect of the renal vein blood of a dog with hypertension due to renal ischemia.[13]

THE LOCAL REGULATION OF BLOOD FLOW BY VESSELS OF NORMAL AND HYPERTENSIVE ANIMALS

In the following experiment it was shown that both normal and hypertensive vessels deprived of both central nervous system connections and circulating blood possess tonus and retain the ability to dilate and constrict actively.

The amputated tails of dogs with hypertension induced by constricting both renal arteries were perfused with Tyrode's solution in the manner previously described for the rabbit's ear. After the state of the vessels became constant, the inlet tube leading to the tail was clamped and the pump stopped for 10 minutes. When the perfusion was reëstablished, the fluid level in the manometer tube fell rapidly, demonstrating that the vessels had

dilated. After a short while the vessels began to constrict, reaching their former state within 30 to 45 minutes (figure 4*A*). The same sequence of events may be observed using the tails of non-hypertensive dogs or the isolated ears of normal rabbits (figure 4*B*).

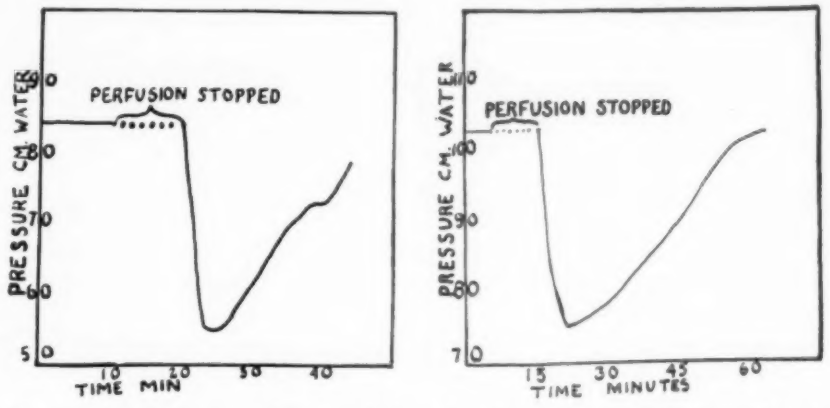


FIG. 4 *A* and *B*. Constant volume perfusion of isolated organs with Tyrode's solution. Effect on vascular tonus of stopping perfusion.

A. Perfusion of amputated rabbit's ear—perfusion stopped for 10 minutes.

B. Perfusion of amputated tail of dog with experimental renal hypertension—perfusion stopped for 10 minutes.

This reaction is undoubtedly similar to the well known phenomenon of reactive hyperemia and it has been previously shown that reactive hyperemia occurs in the denervated human hand.[27] In these experiments the degree of tonicity was not known and it cannot be concluded that hypertonicity was present at the onset of perfusion. They indicate, however, that local changes may be of importance in regulating vascular tonus in tissues of normal or hypertensive animals.

DISCUSSION

In the previous paper * the theory was advanced that hypertension may be due to an increased humoral concentration of a pressor substance produced in the kidneys although other factors such as the integrity of the adrenal gland may play an important rôle. In support of this theory it was shown that extracts prepared from kidneys of patients and animals with hypertension had greater pressor effects than those made from normal kidneys. If this theory were correct one would expect to find an increased concentration of this substance in patients and animals with hypertension and particularly in the renal vein blood of such animals. The vasomotor effects of blood expected to contain such a hypothetical pressor substance was compared with control blood in 39 cases (table 4). In 31 instances differences between the two were noted, and in 23 of these (74 per cent) the hypertensive group was relatively depressor compared with the

* This issue page 1604.

normal. In the three patients with acute glomerulonephritis the blood was comparatively depressor during the hypertensive phase of the disease. Following recovery, when the blood pressure declined to the normal level, the blood became pressor in two instances. These results make it unlikely that hypertension is due to directly acting vasoconstrictor substances such as epinephrine or pituitrin.

TABLE IV

Vasomotor Effects of Blood Expected to Contain a Hypothetical Pressor Substance Compared with Control Blood

Source of Blood with Hypothetical Pressor Substance	Source of Control Blood	Test Object	Action with Respect to Control Blood		
			Pressor	No Diff.	Depressor
Plasma from patients with hypertension	Plasma from patients with normal blood pressure	Perfusion of rabbit's ear	2	5	13
Whole blood from dogs with hypertension	Whole blood from normal dogs	Perfusion of tail of hypertensive dog	1	1	3
Whole blood from dogs with hypertension	Whole blood from normal dogs	Retrograde perfusion of hypertensive dog's leg	2	0	2
Renal vein blood from ischemic kidney of dogs with hypertension	Renal vein blood from normal kidney of dog with hypertension	Perfusion of tail of hypertensive dog	3	0	5
			8	6	23

The failure to find the vasoconstrictor material may be due to one or more of the following factors.

Pickering and Prinzmetal [28] have recently found that renal extracts in certain circumstances may lose their pressor property and have depressor effects. Thus, the material may cause only a depressor effect when injected into rabbits anesthetized with urethane. Epinephrine and other sympathomimetic substances continued to give pressor effects under the circumstances. In this connection Friedman and Abramson [29] observed that renal extracts which raised blood pressure when injected into animals produced depressor effects when perfused through isolated tissues. The preparations were similar to those used in these experiments. It is possible that under the circumstances of the perfusion experiments the vessels were altered so that the renal substance in the blood caused dilatation instead of constriction. This might explain the frequent finding of depressor effects of blood in the hypertensive group.

It is also possible that the substance is not directly pressor in itself but

causes the pressor response after a local change in the vessels. The finding of persistent tonus in denervated hypertensive vessels perfused with Tyrode's solution is in favor of this suggestion. In these experiments, the perfusion was necessarily of relatively short duration. It is possible that more prolonged perfusions are necessary to cause the local change necessary for the constrictor response.

It should be pointed out that the cause of the arterial tonus that constitutes the peripheral resistance in subjects with normal blood pressure is not known. It is not nervous since completely sympathectomized animals may have normal blood pressure.[30, 31] It does not appear to be due to direct effect of a pressor substance in the blood since it has been shown that tonus is present in denervated vessels perfused with Tyrode's solution. Thus our knowledge of the peripheral resistance in subjects with normal blood pressure is in the same position as our knowledge of increased peripheral resistance in subjects with hypertension. It would seem probable that the hypertonus of hypertension is merely an increase of the unknown factor or factors responsible for normal tonus. Whether the kidneys and their pressor substance are concerned in the maintenance of the vascular tonus responsible for normal blood pressure as well as high blood pressure must be left for further investigation.

Conclusions

1. Cross transfusions of large volumes of whole blood between patients with malignant hypertension and persons with normal blood pressure were performed four times. In no instance was there a significant change in blood pressure in either group of subjects.

2. Rabbits' ears were perfused with plasma taken from patients with various types of hypertension and subjects with normal blood pressure. In the majority of instances the plasma removed from hypertensive individuals was relatively depressor.

3. Plasma from a patient with adrenal pheochromocytoma collected during a paroxysm of hypertension had a marked pressor effect on the rabbit's ear preparation. Following removal of the tumor, the blood pressure returned to normal and the pressor effect of the plasma disappeared.

4. The blood from dogs with hypertension due to renal ischemia is no more pressor than that from normal dogs when perfused through the hypertensive dog's own tissues (tail or hind limb).

5. Renal vein blood from the ischemic kidney of dogs with hypertension due to unilateral renal ischemia is not more pressor than that from the unoperated kidney of the same animal when perfused through the dog's tail.

6. Tonus and the ability to dilate and constrict are present in vessels of normal and hypertensive animals deprived of both central vasomotor nervous connections and circulating blood.

7. In 31 instances differences were observed in the vasomotor effects of

blood taken from patients and animals with hypertension as compared with control blood. In 23 of these cases the hypertensive blood was relatively depressor.

The authors want to thank Drs. B. S. Oppenheimer and Harry Goldblatt for their aid and advice.

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TROPICAL AND NONTROPICAL SPRUE (CHRONIC IDIOPATHIC STEATORRHEA): THEIR PROBABLE INTERRELATIONSHIP *

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" For those Aphthae described to us by the ancient founders of Medicine are to us so diverse, that they differ in every climate." (Vincent Ketelaer: " De aphthis nostratibus, seu Belgarum Sprouw," 1669.)

HISTORICAL ASPECTS

THE classic descriptions of Hillary (1759), Manson (1880) and van der Burg (1880) not only established the clinical syndrome of tropical sprue in the medical literature, but served in a sense to establish certain geographical limits within which the disease was normally confined. The original conception that sprue is found only in certain tropical and subtropical climates has been vigorously supported by authorities on tropical medicine and instances in which the syndrome was reported to have appeared elsewhere were regarded as frequently being due to diagnostic error. To quote Manson-Bahr, " One fact may be accepted as certain, that instances of genuine sprue arising *de novo* in permanent residents of temperate Europe usually are very rare and have seldom been recorded." It has of course been long since conceded by these students of the subject that the disease may develop in northern latitudes provided the affected individual formerly lived in the tropics.

The idea that sprue or a disease very closely allied to it might occur with considerable frequency in temperate climates is by no means new. Hanes [19] has called attention to a description of what might well have been sprue in the writings of Aretaeus (first century, A.D.), and Vincent Ketelaer's early account (1669) has been widely quoted. Neither of these descriptions is entirely satisfactory and may be considered subject to individual interpretation. Samuel Gee, who knew of the existence of tropical sprue, was the first to describe (in 1888) a syndrome resembling sprue in children and adults who had never left England. Von der Scheer (1905) noted a similar instance of sprue in a native of Holland. Herter (1908) and Heubner (1910), whose studies were concerned largely with the celiac disease of infancy, made valuable contributions to early knowledge of the physiology of " intestinal insufficiency " and thus indirectly attracted attention to the nontropical forms of sprue.

The history of the sprue syndrome in the United States is of considerable interest. The early observations of Edwin Wood of Virginia and of Simon of New Orleans established the fact that the disease was not infrequently

* Read at Symposium on Medical Problems given at Duke University, Durham, North Carolina, October 13–15, 1938.

seen in natives of the southern states. Later, descriptions appeared from northern hospitals and clinics. References to these accounts and to many other earlier reports of sprue in temperate climates are included in Ashford's bibliography of sprue, which has recently been ably edited by Frederic Hanes.[19] These early accounts appear to have been regarded as medical curiosities and, because of the belief that sprue was essentially a tropical disease, the condition was reported under a variety of diagnoses.

In addition to these reports, a considerable number of patients with the cardinal symptoms of sprue (fatty diarrhea, glossitis, wasting and anemia, and certain metabolic and nutritional disturbances) have been encountered in temperate climates. To the condition in this group of cases the rather unfortunate term "idiopathic steatorrhea" has been given, apparently for the reason just mentioned. This condition has been regarded as occupying an intermediate position between celiac disease and tropical sprue. As more investigators interested in deficiency diseases have become interested in the problem, accounts of such cases have increased almost in geometric progression. Thaysen's monograph (1932) refers to many of the earlier reports and includes his own well-studied cases. Bennett, Hunter and Vaughan also reported a series of 15 cases in 1932; Mackie, a year later, reviewed 71 cases and added one of his own. A rather cursory examination of the literature for the last three years reveals more than 50 additional cases, from such widely scattered sources as Syria, Morocco, Turkey, Italy, Germany, Holland, France, Belgium, Great Britain, the Scandinavian countries and the northern and southern parts of the United States. Some of the more interesting [29, 48, 50, 63] of these recent accounts are cited in the bibliography. Much notable work on the etiology of sprue and its relation to other deficiency diseases and to pernicious anemia has appeared during this period.

Out of the various reports and studies just mentioned, two facts emerge which may be stated about as follows: (1) that tropical sprue, or at least a condition which is virtually indistinguishable from it, has been observed in many portions of the temperate zone in recent years, and (2) that another disease syndrome, differing from tropical sprue chiefly by virtue of its extreme chronicity and an associated tendency to disturbed calcium metabolism and skeletal deformities, has also been described under the heading of "idiopathic steatorrhea."

It has been suggested that this latter condition is essentially a form of celiac disease which continues into adult life and that it is not identical with sprue. Are these conditions, then, fundamentally one and the same, subject only to geographic, racial and climatic variations, or are they independent diseases? Since few have had the opportunity to study both diseases, differences of opinion naturally have arisen. Authorities on tropical medicine incline to the view that sprue and idiopathic steatorrhea are separate diseases, and in this view they are supported by certain English students of the last-named condition. Hess Thaysen [63] in Denmark and Hanes and McBryde in the United States believe that the conditions are identical.

Scope of Present Report and Material on Which Based

The present report concerns itself with "nontropical" sprue or "idiopathic steatorrhea" affecting certain residents of the United States who have been observed during the past ten years at The Mayo Clinic. This condition has been noted with increasing frequency and we now have records of 32 cases in which the presence of the sprue syndrome, with or without various accompanying metabolic disorders, was well established. The affected individuals came chiefly from the central and north central states. Our clinical material is only infrequently affected by visitors from the tropical climates, although we do see occasional instances of "imported" tropical sprue, chiefly in missionaries and physicians on leave from tropical stations.

The material to be reviewed therefore comprises three groups of cases: (1) 14 cases of sprue contracted in the tropics in which the patients were seen at various times thereafter; (2) 10 cases of sprue of nontropical origin, which cases have previously been reported and cited here chiefly because of certain interesting recent developments in these cases, and (3) 22 additional cases of nontropical sprue which have not previously been reported.

No attempt will be made to discuss the voluminous literature on tropical sprue or to describe the disease fully. It would be ridiculous to claim any large experience with it at The Mayo Clinic although the 14 such cases which have been observed here in recent years will be mentioned briefly. The details of six of these cases in which patients were seen during the active phase of the disease are recorded in table 1; the remaining eight patients had what was described as "incomplete sprue" or had been previously treated, with partial or complete success. All of the patients had developed the disease while living in regions where sprue is known to be endemic, and a number of them came to the clinic with a previous positive diagnosis. Seven of the patients were females (ranging in age from 33 to 70 years) and seven were males (whose ages varied from 25 to 66 years). There was no history of significant dietary abnormality in any case, but in each case the usual diagnostic features of glossitis, macrocytic anemia, wasting, flatulent indigestion and fatty diarrhea were, or had recently been, present. The duration of the disease was variable, and the usual tendency toward relapse and remission was noted in certain cases. In five cases effective treatment with liver extract had been begun prior to the patients' registration at the clinic and these patients were well on the road to recovery when seen. In three other cases the diagnosis had been suspected previously and some dietetic or other treatment had been given with partial benefit. In all 14 cases the effects of the disease were evidenced only by the tongue, digestive tract and blood; the chemical, metabolic and nutritional changes seen in nontropical sprue or "idiopathic steatorrhea" were conspicuous by their absence. The typical intestinal pattern as seen on roentgenologic examina-

TABLE 1

Findings in 6 Cases of Tropical Sprue

Age years, sex	Residence	Duration	Diarrhea	Glossitis	Weight lost, pounds	Pigmentation	Hemoglobin, erythrocytes and leukocytes	Smears	Gastric acids	Serum calcium, mg. %	X-ray of small bowel	Stools	Comment
38 M	Hawaii	12 years	Moderate and intermittent	Grade 1	45	Diffuse (racial?)	14.7 3,990,000 6200	Hypochromic anemia	0/16*	8.8	Dilated atonic colon	Typical fatty	Responded well to high protein diet and liver by mouth. Gained 18 pounds. Diarrhea ceased.
37 F	Central America	3 months	Moderate and constant	Definite	30	None	11.6 3,100,000 4700	Macrocytosis	18/36	8.7	Typical disturbances in jejunum and ileum	Typical fatty	Marked improvement on liver extract parenterally. Blood normal 8 months later. Small bowel still showed minor changes.
66 F	Puerto Rico	3 years	Intermittent, not severe	Definite	20	Typical	11.7 3,150,000 5700	Macrocytosis	refused		Not done	Fatty	Diagnosed sprue in Puerto Rico. Some liver extracts at long intervals with relief.
56 M	India	12 years	Intermittent	History only	50	None	12.1 3,400,000 4800	Macrocytosis	0/4 (with histamine)		Negative; in remission	Fatty (history only)	Diagnosed sprue in India. Successfully treated with diet; then relapse. Improved rapidly on liver extract (intramuscularly). Blood normal three months later. Neurologically negative.
54 M	Philippines	4 years	Intermittent and severe	Atrophic tongue	23	None	7.1 1,570,000 3900	Macrocytic anemia, Vol. index 1.1	84/76 (with histamine)	8.0	Not done	Fatty (history only)	No response to extralin but prompt improvement on liver extract (intramuscularly). Well 2½ years later. Neurologically negative.
25 M	Nicaragua	15 months	Constant and severe	History only	23	None	9.0 2,120,000 6000	Macrocytosis Vol. Index 1.2	22/38		Not done	Fatty	Excellent response to liver extract by mouth. Reticulocytes rose to 11%. Neurologically negative.

* 0 = free HCl, 16 = total acidity.

tion was noted in certain cases. Treatment with liver extract was effective in each of these cases, the results being in some instances quite comparable to those noted in pernicious anemia.

Nontropical Sprue

To avoid confusion in the discussion to follow, some arbitrary definition of terms will be attempted here: The "sprue syndrome" as used hereafter will refer to the disease picture mentioned in the previous paragraphs without reference to its geographic origin; "nontropical sprue" will refer to the same syndrome as seen in natives of temperate climates without reference to the development of any complicating nutritional or metabolic disorders. "Idiopathic steatorrhea" will be used synonymously with "nontropical sprue."

Ten Cases of Nontropical Sprue Previously Reported

The essential clinical data in this group of cases are recorded in tables 2 and 3 (Cases 1 to 10, inclusive). Nine of these patients were residents of the North Central States; one was from Texas. Two of the patients had been born in Northern Europe but had spent their entire adult lives in the United States. Five were women, five were men. Their ages varied from 26 to 51 years, and the duration of symptoms varied from nine months to 30 years. The presenting symptoms in this group of cases included weakness, diarrhea, abdominal cramps, flatulent indigestion, and diarrhea of variable severity. Among the striking physical findings were evidence of extreme loss of weight and of muscular wasting, glossitis with local areas of atrophy of the tongue, abdominal distention, deformities of the skeleton, stunted growth, peripheral edema and tetany. It may be mentioned here that Cases 1, 2, 4, and 8 which were reported separately at an earlier date, have been reviewed and commented on by various authorities on so-called idiopathic steatorrhea and have been regarded as acceptable examples of the condition. To see these cases in their proper relation to the picture as a whole it is necessary to turn to the more recently studied group of 22 cases, the details of which are likewise found in tables 2 and 3 (Cases 11 to 32, inclusive), and to consider the subsequent developments in certain of these earlier cases.

Entire Series of Thirty-Two Cases of Nontropical Sprue

To attempt to give a clinical picture of the series as a whole requires a general consideration of the symptoms and signs of the disease, since it is only in this manner that the "irregularly progressive" character of the condition, as noted by Ashford, can be appreciated. As Castle and his associates have also noted, tropical sprue does not present a static, but a dynamic, condition and this statement applies with equal force to the disease as seen in nontropical climates.

TABLE II

Clinical Findings in 32 Cases of Nontropical Sprue

Case	Age in years, and sex	Duration	Diarrhea	Infantilism	Edema	Bony deformity	Tetany, active or latent	Glossitis	Weight lost, pounds	Amenorrhea present	Pigmentation	X-ray findings	Comment
1	31 F	Lifelong; worse last 7 years	Episodic; grade 2–3	Grade 2	None	Rachitic stigmas	Active, grade 3	Slight	45	+	Definite	None	Living and well. High protein diet and calcium, viosterol.
2	33 F	Lifelong; worst last 6 to 7 years	Episodic; lifelong	Grade 1	None	Marked osteomalacia	Active, grade 2	None	40	+	Definite eruption resembling pellagra	None	Died. No benefit from diet, calcium.
3	51 F	20 years plus	2–3 yrs. moderate	Grade 1	None	None	Active, grade 4 +	None	20	Menopause	Slight; urticaria	None	No benefit from treatment (no recent record).
4	47 F	20 years	Episodic; 20 years	Grade 2	Grade 2	None	Seasonal; active at times for 20 years	Grade 1	25	+	Slight	Jejunitis	Effectively treated. Living and well (see appendix A).
5	47 M	10 years plus	Episodic; 10 years	None	Grade 2	None	Active for 10 years	Grade 1	50		Slight	Jejunitis	Living and well. Liver extract by mouth with benefit.
6	44 M	9 years	1 year; grade 3	None	Grade 1	None	None	Grade 1	26		None	Jejunitis	No benefit from treatment (no recent record).
7	45 F	15 months	Grade 3	? small frail type	Grade 2	None	Latent; one active attack	Grade 1	22	+	None; marked pruritus	Jejunitis and ileitis	Died; hemorrhagic diathesis. Prothrombin deficiency?
8	26 M	10 years	Grade 1 to 2	Grade 2	Grade 1	Rachitic stigmas; osteoporosis	None	Grade 1	20		Slight	Jejunitis and ileitis	At first marked benefit from parenteral liver extract; later this was ineffective. Died of exhaustion.
9[1]	47 M	6 years	Occasional severe episodes, grade 1 to 2	None	Grade 1	None	None	Grade 1	70		Eczema of hands	Jejunitis and ileitis	Indifferent response to treatment. Died at home; cause unknown.
10	44 M	12 years	Slight; irregular	None	Grade 1	None	None	Slight	18		Extensive, brownish	Ileitis slight	Good response to liver treatment.

TABLE II (*continued*)
Clinical Findings in 32 Cases of Nontropical Sprue

Case	Age last years, and sex	Duration	Diarrhea	Edema	Tetany, active or latent	Glossitis	Weight lost, pounds	Amenorrhea	Pigmentation	Blood pressure	Comment
11	56 M	4 months	Grade 2+	None	None	Grade 2	30+		None	122/75	Reticulocytes rose to 5.1% on liver extract. Blood normal 5 months later. Gained 20 pounds.
12	49 M	5+ years	Grade 2+ (intermittent)	None	None	Grade 1 (mild)	25+		Slight, yellowish	108/80	Liver extract given intramuscularly; gained 40 pounds. RBC normal 1 year later.
13	32 M	6 years	Grade 2 (intermittent)	None	None	Grade 1	30+		Diffuse, yellowish	110/70	No benefit from jeculin but immediate response to liver extract (intramuscularly); gained 25 pounds. Well after 4 years.
14	60 M	9 months	Grade 2	Grade 2	None	Grade 1	32+		None	110/70	Reticulocytes rose to 10%. RBC up 2½ million; liver extract parenterally. Rapid improvement. Diarrhea controlled.
15	23 F	2 years	Grade 3	Previously	None	Grade 1	24+	+	Slight, diffuse	84/52	Considerable liver extract with slight improvement, but reticulocyte rise did not exceed 4%.
16	44 M	3 years+	Grade 3	Definite	None	?	53+		Slight, diffuse	95/60	Never been well. Little or no effect from adequate liver. Diarrhea not controlled. Blood slightly improved. Died later at home. Marked bony deformity.
17	38 F	2 years	Grade 2	None	None	Atrophic tongue	10+	No	Diffuse melanosis, grade 3	116/70	No response to provocative test for Addison's disease. CNS negative. Marked improvement on liver extract; gained 10 pounds.
18	63 F	6 years	Moderate (intermittent)	None	None	Atrophic tongue	Indeterminate, regained on treatment	No	None	130/85	Sore tongue, anemia and diarrhea. Responded to liver extract. Relapse twice followed its discontinuance. Felt fairly well when last examined.
19	26 M	5 years	Grade 2	None	None	Not marked	27		Diffuse pigmented eruption on legs	102/74	Reticulocytes rose to 11% and marked improvement in small bowel occurred on 20 day period on liver extract. Relapse followed discontinuance of treatment here.
20	37 M	13 years	Grade 2+ (intermittent)	None	None	Marked with aphthous stomatitis	18		Slight?	120/85	Under observation here for 13 years. Previously benefited by sprue diet. Improved on liver extract. RBC up to 5,000,000.
21	17 M	1+ years	Variable; never severe	Grade 2	None	Grade 1	20		Diffuse, brownish	110/60	Good response to liver extract and vitamin concentrates. Doubled weight in two years.

TABLE II (*continued*)

TABLE II (*continued*)

Clinical Findings in 32 Cases of Nontropical Sprue

Case	Age in years, and sex	Duration	Diarrhea	Edema	Tetany, active or latent	Glossitis	Weight lost, pounds	Amenorrhea	Pigmentation	Blood pressure	Comment
22	30 M	4 years	Grade 3+	None	None	Grade 3	43		None	102/82	Good response to liver, but apparently discontinued treatment. Died of exhaustion and complicating mastoiditis.
23	56 M	1+ year	Grade 3	Grade 2+	None	Marked	26		Marked	90/56	Fatty stools and severe glossitis indicated sprue. Good immediate response to liver, but discontinued it and died two years later in relapse.
24*	41 M	3+ years	Grade 3	None	History of previous attack	Grade 1	30		Grade 2	92/56	Liver by mouth inadequate response, good response extract intramuscularly (practically well 5 months later). Roentgen-ray of small bowel showed improvement.
25	44 M	4 years	Grade 3	Slight, variable	Latent	Grade 3	69		None	100/60	Improved on liver extract. Still has some bone pains (osteoporosis?).
26	37 M	3 years	Grade 2+	None	None	Grade 2	21		None	105/70	Good response to liver intramuscularly. Blood normal 8 months later. Still has diarrhea at times.
27	50 M	3 years	Grade 2	None	None	Marked	17		None	120/78	Indifferent response to vigorous liver treatment. Blood improved only slightly. Patient seemed to be slowly failing.
28	53 M	1 year	Grade 2	None	None	Grade 1	20		Slight	104/60	Indifferent response to vigorous liver treatment but later definite improvement. Mild relapse 18 months later although still taking liver.
29†	29 F	4 years	Grade 3	None	None	Grade 1	23	+	Diffuse yellowish	96/76	Some liver extract (not enough) without benefit. Complicating t. b. lymphadenitis. Died. Necropsy.†
30	54 M	3½ years	Grade 2+	Grade 2	Active at times	Very slight	10		None	90/56	Improved on liver extract but bowel did not clear up entirely. Excess fat in stools at various times. Sudden death from Landry's paralysis. Blood normal before death. Necropsy.
31	49 M	20+ years	Intermittent	None	None	None	Variable		Slight	106/76	Always had irritable intestinal tract. Remarkable general improvement on liver extract intramuscularly with restoration of blood.
32	71 F	10+ months	Grade 3	None	None	Slight	37	No	Definite	90/70	Liver extract and transfusions failed to control. Blood concentration before death. Diarrhea continued. Died of exhaustion.

* See appendix B.

† Case reported in detail by Bargen and Mendez Ferreira.[43]

TABLE III

Laboratory Findings in 32 Cases of Nontropical Sprue

Case	Hemoglobin*	Erythrocytes	Leukocytes	Erythrocytes, morphology	Gastric acidity		Stools	Serum calcium, mg. per 100 c.c.	Serum phosphorus, mg. per 100 c.c.	Serum bilirubin, mg. per 100 c.c.	Serum protein, gm. per 100 c.c.	Plasma cholesterol, mg. per 100 c.c.
					Free HCl	Total						
1	54	3,620,000	6,800	Macrocytic anemia	40	56	Oil or fat in excess	6.3 to 11.3	4.4 to 6.6			
2	54	3,370,000	2,700	Not examined; vol. index 0.88	18	38	Oil or fat in excess	6.3 to 8.2	2.3 to 4.5			
3	56	3,420,000	11,000	Vol. index 1.03	20	32	Fatty	4.9 to 7.7	2.4 to 4.6			
4	38	3,710,000	4,900	Hypochromasia	40	62	Oil or fat in excess	6.3 to 11.6	4.0 to 4.1		4.1 to 5.0	139
5	64	4,000,000	6,500	Hypochromic anemia	42	56	Oil or fat in excess	6.8 to 8.6	2.9 to 3.9		4.4 to 5.3	
6	64	3,250,000	5,100	Macrocytic anemia	58	64	Oil or fat in excess	8.0 to 10.5	2.2 to 3.4			103
7	67	7,790,000	5,600	Macrocytic anemia	46	58	Fat in excess	6.8 to 9.0	2.8 to 3.0		4.8 to 6.1	
8	62	2,580,000	2,700	Macrocytic anemia	22	38	Fat in excess	7.8 to 8.7	3.5 to 4.9	1.1 to 1.3	4.9†	93
9	50	2,850,000	2,300	Hypochromasia; eosinophilia	36	46	Fat in excess	8.5 to 10.4	3.6 to 4.2	1.0	5.6 to 5.9	
10	70	3,510,000	3,100	Macrocytic anemia	38	50	No fat in excess with low fat diet	9.5	4.2		7.3	

TABLE III (*continued*)

Laboratory Findings in 32 Cases of Nontropical Sprue

Case	Residence	Hemoglobin, erythrocytes, leukocytes	Erythrocytes, morphology	Gastric acidity		Stools	Serum calcium average ‡	Serum phosphate average ‡	Serum bilirubin average ‡	Serum protein average §	Plasma cholesterol average ‡	Basal metabolic rate	Roentgen-ray		Miscellaneous data
				Free HCl	Total								Bowel	Bones	
11	Tennessee	13.6 2,780,000 7500	Macrocytic anemia	56	64	Fatty	9.1	4.7	1.2 (ind.)		141		Diffuse ileitis	Neg.	CNS negative.
12	Missouri	10.2 2,600.000 4700	Macrocytic anemia			Fatty	7.9	2.7	1.0				Small bowel not examined. Colon neg.	Neg.	
13	Iowa	11.7 2,680,000 3200	Marked variation in size and shape; vol. index 1.15.	0 (with histamine)	6	History of fatty stools								Neg.	CNS negative.
14	Tennessee	10.7 2,290,000 5900	Macrocytic anemia	22	30	Described as fatty				5.4			Typical changes	Neg.	
15	Missouri	9.5 3,690,000 6000	Macrocytosis	0 (Ewald)	4	Variable; fatty at times. Ate very little	6.9	2.3		5.4	82		Typical changes	Osteoporosis	Purpuric eruption at times, relieved by transfusion.
16	Montana	5.5 2,950,000 5000	Indeterminate hypochromasia	0 (Ewald)	20	Variable; fatty at times. Ate very little	7.9	3.9	1.0	3.5	87		Typical diffuse involvement	Osteoporosis, grade 3. Scoliosis	Died.

TABLE III (*continued*)

Laboratory Findings in 32 Cases of Nontropical Sprue

Case	Residence	Hemoglobin, erythrocytes, leukocytes	Erythrocytes, morphology	Gastric acidity		Stools	Serum calcium average‡	Serum phosphate average‡	Serum bilirubin average‡	Serum protein average§	Plasma cholesterol average‡	Basal metabolic rate	Roentgen-ray		Miscellaneous data
				Free HCl	Total								Bowel	Bones	
17	South Dakota	8.0 3,850,000 3500	Macrocytes and hypochromasia	26	46	Variable; had been fatty	8.7		1.2	6.6			Diffuse changes	Slight osteoporosis	Melanotic pigmentation. Joint pains.
18	Kentucky	14.4 4,870,000 9200	Occasional macrocyte	14	40	History of fatty stools. Normal when examined	9.9			7.4		−7	Normal	Negative	Prothrombin 47% normal.
19	Kentucky	11.1 2,440,000 6000	Macrocytic anemia	58	64	Very fatty	9.0	2.8		7.8	119		Typical changes	Osteoporosis	Pigmented skin lesions on legs. Subacute combined degeneration.
20	Texas	9.3 2,470,000 10,800	Macrocytic anemia	12	22	Fatty	8.8						Typical changes		
21	Michigan	10.8 2,690,000 3000	Macrocytic anemia	42	60	Fatty	9.5		3.1		104			?	History of bone pains and greenstick fracture.
22	Missouri	13.6 4,350,000 9700	Hypochromasia	0 (with histamine)		Described as voluminous and fatty	9.3		1.2					?	
23	Wisconsin	9.2 1,890,000 4400	Macrocytic anemia			Fatty									

* Hemoglobin in gm. per 100 c.c.; erythrocytes and leukocytes per cubic millimeter of blood.
† See text. Case previously studied by Weir and Adams.
‡ Milligrams per 100 c.c.
§ Grams per 100 c.c.

TABLE III (*continued*)

Laboratory Findings in 32 Cases of Nontropical Sprue

Case	Residence	Hemoglobin, erythrocytes, leukocytes	Erythrocytes, morphology	Gastric acidity		Stools	Serum calcium average‡	Serum phosphate average‡	Serum bilirubin average‡	Serum protein average§	Plasma cholesterol average‡	Basal metabolic rate	Roentgen-ray		Miscellaneous data
				Free HCl	Total								Bowel	Bones	
24	Minnesota	6.6 2,860,000 9600	Macrocytic anemia	40	54	Fatty	8.9			6.3	150	+11	Typical changes	Osteoporosis	
25	Illinois	14.1 3,980,000 5100	Macrocytosis	8	16	Fatty	5.3	1.3		5.5			Diffuse enteritis		Peripheral neuritis. (Crossed leg palsy?)
26	Alabama	11.1 2,800,000 5800	Macrocytic anemia	6	12	Had been fatty						−6			
27	Illinois	11.4 3,600,000 8900	Macrocytic anemia	68	70	Fatty	8.8	3.3					Typical changes		Normal enzymatic activity in duodenal contents.
28	Kansas	14.5 3,640,000 6100	Macrocytic anemia	0 (with histamine)		Fatty	7.6	2.7		6.3			Typical changes	Slight osteoporosis	Normal enzymatic activity in duodenal contents.
29	Wisconsin	11.1 3,590,000 16,000	Macrocytosis	0 (with histamine)		Fatty	7.6			4.2	92		Typical changes		Normal enzymatic activity in duodenal contents.
30	||	15.4 4,360,000 5600	Some persistent macrocytosis	0 (with histamine)		Fatty	7.9	3.0	1.0 (ind.)	5.2	158		Typical changes		Sprue diet + calcium therapy prior to admission.
31	¶	12.5 2,790,000 4500	Macrocytic anemia	36	40	Fatty at times	9.3		1.2	5.1 (rose to 7.1 in 60 days)	145		Normal		Normal enzymatic activity in duodenal contents.
32	Kansas	14.1 3,650,000 9600	Macrocytosis	0 (with histamine)		Voluminous and fatty at times	7.9						X-ray not satisfactory		

|| Marine engineer, but has not been in tropics in past 10 years.
¶ Had lived in China but had symptoms of sprue before going there.

Symptoms. All of the 32 cases of nontropical sprue of this series have certain features in common, although not all of these symptoms were present in every case at each individual period of study. These common features are glossitis and stomatitis, emaciation, fatty diarrhea, various types of anemia, disturbances of the metabolism of calcium and of protein, and a group of symptoms related to various vitamin deficiencies. These will be discussed in detail in later paragraphs.

There are no definite prodromal symptoms of nontropical sprue, although certain patients who later had the full-blown disease gave a history of chronic remittent gastrointestinal disturbances, nausea, vomiting, anorexia, intolerance to food, and intestinal irritability. In spite of these complaints it was difficult or impossible to uncover a history of dietary errors in most of these cases and, in fact, with one or two exceptions a normal mixed diet had been taken more or less regularly up to the time symptoms appeared. As will be noted from tables 2 and 3, the course of the disease was extremely chronic and a majority of the patients were seen three or more years after the onset of the earliest definite symptom, usually diarrhea. Remissions and relapses punctuated the progress of the disease in most instances thereafter. Nausea and vomiting, or what had been taken to be an infectious gastroenteritis, were frequently mentioned as an early complaint. Diarrhea, at first intermittent and later more or less continuous, was the next common development. Stools were often described as brown, watery and offensive at the onset; later, voluminous, foul, yellow-gray, fatty stools were noted. As the diarrhea became more severe, abdominal cramps and flatulent dyspepsia became increasingly troublesome. Loss of weight and weakness were usually progressive and extreme. Glossitis and stomatitis of such severity as to produce definite symptoms were described by 24 of the 32 patients. The oral lesions were not always continuously present and were not necessarily active at the time of examination. Pallor and cutaneous pigmentation were occasionally mentioned. More than half the patients complained of bone and joint pains, which in many cases was an early and annoying symptom. Amenorrhea was noted by six of the seven female patients between the ages of 18 and 45 years. Tetany, which was almost invariably related to exacerbations of the diarrhea, was noted by nine patients and dependent edema was a rather conspicuous feature of the disease in 11 cases.

Physical Examination. Physical examination revealed as its most striking finding a remarkable degree of malnutrition with muscular wasting and cachexia. Losses of 30 pounds (13.5 kg.) or more were extremely common. Many of the patients had a peculiar mummy-like appearance with definite, diffuse, yellowish-brown pigmentation of the skin (figure 1). Lack-luster hair, club fingers and brittle nails were common; a distended and flatulent abdomen was almost an invariable finding. The appearance of the tongue and mouth varied considerably. Moderate atrophy with redness of the tip and edges of the tongue was most commonly seen, but in

certain cases diffuse stomatitis or definite aphthous lesions of the tongue and mouth were noted.

In addition to these signs, certain nutritional disturbances and deficiency syndromes were observed as complications of the original disease. Pellagrous skin eruptions were noted in two cases (figure 2). In other cases an itching, pigmentary dermatitis of patchy distribution developed. Petechial hemorrhages were observed in two cases. Edema was noted in 11 cases; it was usually confined to the lower extremities and in only one case did ascites develop (Case 8). Infantilism, bony deformities (including scoliosis, knock-knee and rachitic stigmas) and stunting of growth were

FIG. 1. Melanotic pigmentation of the skin in sprue. In this case the presence of Addison's disease was excluded by metabolic studies performed during a period of salt deprivation.

noted in five cases, and osteoporosis was seen in these and in four additional cases. In three cases a diagnosis of subacute combined degeneration of the spinal cord was made by consulting neurologists. One patient had a transient polyneuritis associated with pellagra. Nine patients had definitely positive Chvostek's and Trousseau's signs at the time of examination. Cataracts, which have been mentioned by other writers, were not seen in this series of cases, but a slit-lamp examination was not routinely carried out. Some of the significant "complications" are given in table 4; their nature will be discussed later.

FIG. 2. Subsiding pellagrous dermatitis (see Case 4 in appendix).

TABLE IV

"Complications" or Late Sequelae of the Sprue Syndrome

Complication	Number of cases
Infantilism	4
Bony deformities or fractures	4
Osteoporosis	9
Tetany	9
Amenorrhea	6
Edema (hypoproteinemia)	11
Hemorrhagic features	2
Subacute combined degeneration	3
Polyneuritis (pellagra)	1

Vitamin Deficiencies. As mentioned in an earlier paragraph, one of the significant features of sprue as seen in temperate climates is the multiplicity of vitamin deficiencies which may develop, presumably because of failure of absorption of these substances in the digestive tract. For obvious reasons the fat-soluble protective substances are most likely to be affected. A deficiency in the absorption of vitamin A, as shown by night blindness and xerosis conjunctivae, has been described (Riddell). Malabsorption of

vitamin D may be inferred from the calcium deficiencies previously mentioned and the development of osteoporosis, osteomalacia and tetany. Linder and Harris showed that the administration of vitamin D alone was of considerable clinical value, an observation which has been fully confirmed by others. No data are available on the utilization of vitamin E. One of our patients (Case 1) went through a normal pregnancy after the steatorrhea and calcium deficiency had been brought under control. The absorption of the most recently discovered fat-soluble vitamin, vitamin K, may conceivably be adversely affected by any type of sprue. A hemorrhagic diathesis has been described in connection with tropical sprue, and one of our patients (Case 7) died at home in a manner strongly suggestive of prothrombin deficiency. In one other case recently observed the normal prothrombin content of the plasma was reduced by more than 50 per cent. Further studies on vitamin K absorption in cases of sprue may lead to elucidation of the curious hemorrhagic state which may cause a fatal termination of the disease.

Data on the absorption of the water soluble vitamins are by no means complete. The antineuritic vitamin (vitamin B_1) is absorbed at least to the point where peripheral neuritis is prevented in the majority of cases. The daily requirements of the vitamin are, however, obviously increased by the diarrhea. The pellagra-preventing factor may be poorly assimilated in certain cases, as indicated by our two patients with pellagrous skin lesions (Cases 2 and 4). The absorption of other factors in the vitamin B complex has not as yet been thoroughly studied but, as Castle and Rhoads and their associates suggested, a failure of utilization may be intimately and fundamentally concerned with the etiology of the disease. Little information is available as to the absorption and utilization of vitamin C. We have studied the concentration of this material in blood and urine in a few cases and obtained results which fell within the limits of normal.

It should again be emphasized at this point that one of the significant differences between tropical and nontropical sprue has to do with the number and variety of avitaminoses which have been reported in the latter condition. The recently reported case of Fullerton and Innes is an excellent example of this phenomenon.

Laboratory Data. Stools. No better description of the typical stools in sprue can be offered than that of Samuel Gee: "Signs of the disease are yielded by the feces; being loose, not formed, but not watery; more bulky than the food taken would seem to account for; pale in colour, as if devoid of bile; yeasty, frothy, an appearance probably due to fermentation; stinking, the stench often very great, the food having undergone putrefaction rather than concoction." It should not be inferred that all stools are of this kind in either tropical or nontropical sprue or that diarrhea is a constant and invariable symptom. At various times fairly normal or even constipated stools may be passed whereas, at other times, a watery diarrhea is temporarily conspicuous.

The stools in this series of 32 cases of nontropical sprue yielded large amounts of fat on analysis, but the degree of steatorrhea varied considerably with the stage of the disease and the patient's diet. Many of the patients observed at the clinic had learned to restrict their intake of fat which of course tended to control the diarrhea and alter the chemical composition of the stools. Chemical examination of the stools was not carried out routinely in this series of cases and the diagnosis of steatorrhea was based in many instances on microscopic examination of specimens stained for fat. The degree of loss of fat was obviously variable, but in many specimens 30 per cent or more of the dried stool consisted of fat. Thaysen's [62] patients, who were on a high fat diet, lost from 13 to 27 per cent of the fat ingested; most of the chemical analyses made in cases in this series fell within this range. The patient in Case 8, whose fat tolerance was studied by Weir and Adams and who was on a fat intake of 45 gm. per day, lost approximately one-third of this amount in the stools. The patient previously reported from the clinic (Case 29) by Mendez Ferreira and Bargen, excreted 62 gm. of fat in one day on an intake of 65 gm. In some of our earlier cases the tolerance to fat in the diet was low, not exceeding 40 to 50 gm. daily. Stools contained chiefly split or neutralized fat, a finding which has been reported by many other observers.

Blood. Three types of anemia have been described in nontropical sprue: (1) a hypochromic or secondary form; (2) a hyperchromic, macrocytic type, in which the morphologic features of the formed elements of the blood are almost identical with those seen in pernicious anemia, and (3) an erythroblastic type. As Thaysen and others have mentioned,[29, 30, 48, 62] the hematologic picture is not necessarily constant in any given case, being modified by the course of the disease and by treatment. In our earlier group reported from the clinic [58] (Cases 1 to 10, tables 2 and 3) half of the 10 patients had a typical macrocytic anemia. In the second group (Cases 11 to 32) 17 of the 22 patients showed a similar picture. Four patients had a moderate to marked hypochromasia, with variations in the size, shape and staining properties of the erythrocytes. In one other case (Case 30) the stained smears of the blood showed many nucleated red cells and Howell-Jolly bodies, a finding which was explained by the extreme atrophy and fibrosis of the spleen at necropsy. It is interesting to compare the hematologic findings in our series of cases (table 5) with the report of Fairley

TABLE V

Blood Findings and Gastric Acidity

	Old series (10 cases)	New series (22 cases)
Average hemoglobin (gm. per 100 c.c.)	9.6	10.2
Erythrocyte count (millions per cu. mm.)	3.41	3.3
Achylia (6 cases checked with histamine)	0	8
Macrocytic hyperchromic anemia	5	17 cases
Hypochromic anemia	5	5 cases

and his colleagues [14] on the blood in tropical sprue. The average values for hemoglobin and erythrocyte counts are almost identical. Abnormal levels of bilirubin in the blood were not noted in this series of cases. Leukocytosis was rare except in the presence of complications.

We did not have an opportunity to perform biopsies of the bone marrow in any case of this series. These have been described in sprue by others (Castle and associates [10]), however, and Thaysen,[62] in studying nontropical sprue, has noted a red bone marrow with megaloblastic regeneration. In the late stages of the disease a hypoplastic bone marrow has been encountered.

Gastric acidity. Free hydrochloric acid was demonstrated at one time or another in all of the 10 cases previously reported (Cases 1 to 10), although it was often necessary to use histamine as a stimulant to demonstrate it. In the second series of 22 cases (Cases 11 to 32), eight patients had a lack of hydrochloric acid at the time of examination; in six of these cases the finding persisted after stimulation with histamine. Two patients refused gastric analysis. These figures correspond roughly with those of Castle and Rhoads and their associates [10] who found anacidity in about 30 per cent of their cases of tropical sprue. Because of the possibility of pancreatic dysfunction in certain of our cases, the duodenal content was studied for enzymatic activity in six cases. In each case normal values for lipase, trypsin and amylase were found.

Calcium and Phosphorus Metabolism. The relatively high incidence of tetany, osteoporosis and skeletal deformity has already been mentioned. These conditions obviously depend on long-continued losses of calcium from the organism. It has been shown by Marble and Bauer that a positive calcium balance can be obtained in the presence of steatorrhea with a high intake of calcium, whereas with a low intake of calcium a negative balance prevails. Diarrhea increases fecal calcium losses, as might be expected, the urinary excretion of calcium remaining unchanged.

Roentgenologic examination of various bones was carried out in a number of cases and, in nine, definite osteoporosis was demonstrated. The two patients who showed the most striking skeletal defects (Cases 2 and 16) both had marked scoliosis and kyphosis of the degree one might expect to see in osteomalacia (figure 3). Roentgenologic studies of the bones of these patients showed osteoporosis, deformities of the pelvis and long bones, and pseudofractures (" umbauzonen ").

As Fairley and others [11] have noted in tropical sprue, slight reductions in the blood calcium (1 to 1.5 mg. per 100 c.c.) were common. Such slight abnormalities were noted in 19 cases in our series whereas, in nine other cases with latent or active tetany, the average level of blood calcium was approximately 6 mg. per 100 c.c. The serum phosphorus was always lowered in this group of cases, thus differentiating this form of tetany from that of parathyroid insufficiency. Phosphatase activity of the serum was within normal limits in the few cases studied.

FIG. 3. Skeletal osteoporosis and associated skeletal deformities in untreated sprue (Case 16).

Chemical and Metabolic Disturbances. A flat blood sugar curve after the oral administration of glucose has been described in cases of nontropical sprue by Thaysen [62] and Hansen [21, 22] and in native tropical sprue by Fairley.[11] We have noted abnormal glucose tolerance curves of this type in five of our cases of nontropical sprue (figure 4); a normal curve was found in one other case in which the patient was under treatment. Thaysen [62] noted that a normal hyperglycemia was the rule if glucose was given intravenously or if epinephrine was administered to patients with tropical sprue, and he argued from these observations that some endocrine disturbance must be postulated in order to explain this seeming contradiction

in carbohydrate metabolism. Fairley [11] and others felt that decreased absorption from the intestine explained the lack of alimentary response, while a failure of insulin production incident to starvation might account for the hyperglycemia when glucose was given by vein. The relation of the absorption of vitamin B_1 to these disturbances in carbohydrate metabolism has not been investigated.

In our series of cases of nontropical sprue a reduction in the blood cholesterol proportionate to the severity of the steatorrhea was commonly observed. Fairley [11] previously noted a similar effect in tropical sprue. Barker and Rhoads have recently demonstrated an absence of the usual rise in blood lipids after a fat meal in cases of sprue, indicating failure of intestinal absorption. This abnormality was corrected following the administration of liver extract. This malabsorption of fat is, of course, the

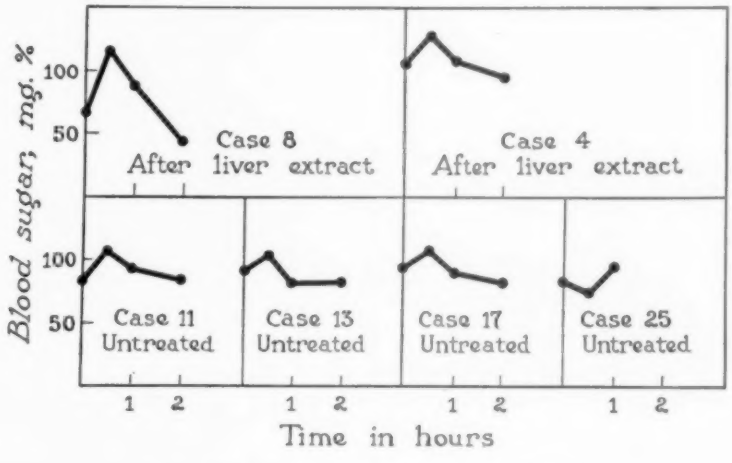

FIG. 4. Glucose tolerance curves in sprue.

most obvious explanation of the phenomenon of steatorrhea, but other investigators, notably Bauer and Moncrieff and Payne, have suggested an active elaboration and excretion of fat from the bowel.

Little is known about nitrogenous metabolism in sprue, but it has been noted that moderate azotorrhea may occur. This is considerably less than that noted in pancreatogenous steatorrhea, a fact which may distinguish the two conditions. One patient (Case 8) was barely in nitrogen balance during one attack of diarrhea but stored nitrogen while under treatment later. It seems probable that some losses of nitrogen must occur through the stools and that, in addition, there may be deficient absorption of protein and protein-forming substances from the intestinal tract of these patients. As previously mentioned, 11 of our 32 patients had edema which was associated with a low serum protein and a normal or reversed albumin-globulin ratio. In 18 cases in which the serum protein was determined, the range was from

4.1 to 7.8 gm. per 100 c.c., or an average of 5.5 gm. Fairley's [11] figures for tropical sprue were somewhat higher (table 6).

It is interesting to note that an elevated metabolic rate has been regarded as a diagnostic feature of nontropical sprue (Thaysen,[62] Hansen [21, 22]). How reliable this is may be questioned, since starvation alone may elevate the rate. My own data are not sufficient to warrant an opinion on the point.

Roentgenographic Studies of the Intestinal Tract. The one explanation which would serve to include all the various reported disturbances in the metabolism of carbohydrates, proteins, fats and calcium in the sprue syndrome is, as has been mentioned previously, failure of absorption from the intestinal tract. The idea of intestinal dysfunction in sprue is by no means new, and it has received some support from pathologic observations as well as from recently reported roentgenologic studies of the small bowel. Such studies have been reported by Camp and me, by Mackie and his coworkers,[38, 39] and by Miller and Barker. The characteristic picture is that of delayed motility and alteration in the mucosal relief of the small intestine, especially the jejunum; the contour of the lumen of the bowel is smoothed out, the usual markings of the valvulae conniventes are obliterated and the barium is clumped in elongated masses (figure 5). Dilatation of the colon and loss of its usual haustral markings are often conspicuous. Not enough other deficiency diseases have been studied roentgenologically in this manner to warrant any conclusions as to the specificity of these findings; Camp has noted a similar appearance in the case of a pellagrous patient and in that of a child with celiac disease. Pancreatogenous diarrhea has in three cases personally observed by me produced a similar effect, and Ravdin and his collaborators [51, 53] have noted that the small bowel may assume the appearance of hypomotility and altered mucosal relief after a meal of olive oil. Possibly the malabsorption of fat is the sole responsible factor in the production of these changes in intestinal motility and contour.

TABLE VI

Blood Chemical Data

	Cases	Reading per 100 c.c.	
Serum bilirubin	10	1.5 mg. or less	
Blood cholesterol	13	82–158 mg.	(range)
		123 mg.	(average)
Serum proteins	18	4.1–7.8 gm.	(range)
		5.54 gm.	(average)
Serum calcium	9*	4.9–6.9 mg.	(range)
		6.13 mg.	(average)
	19**	7.6–10.0 mg.	(range)
		8.7 mg.	(average)

* Patients with active or latent tetany.
** Other patients.

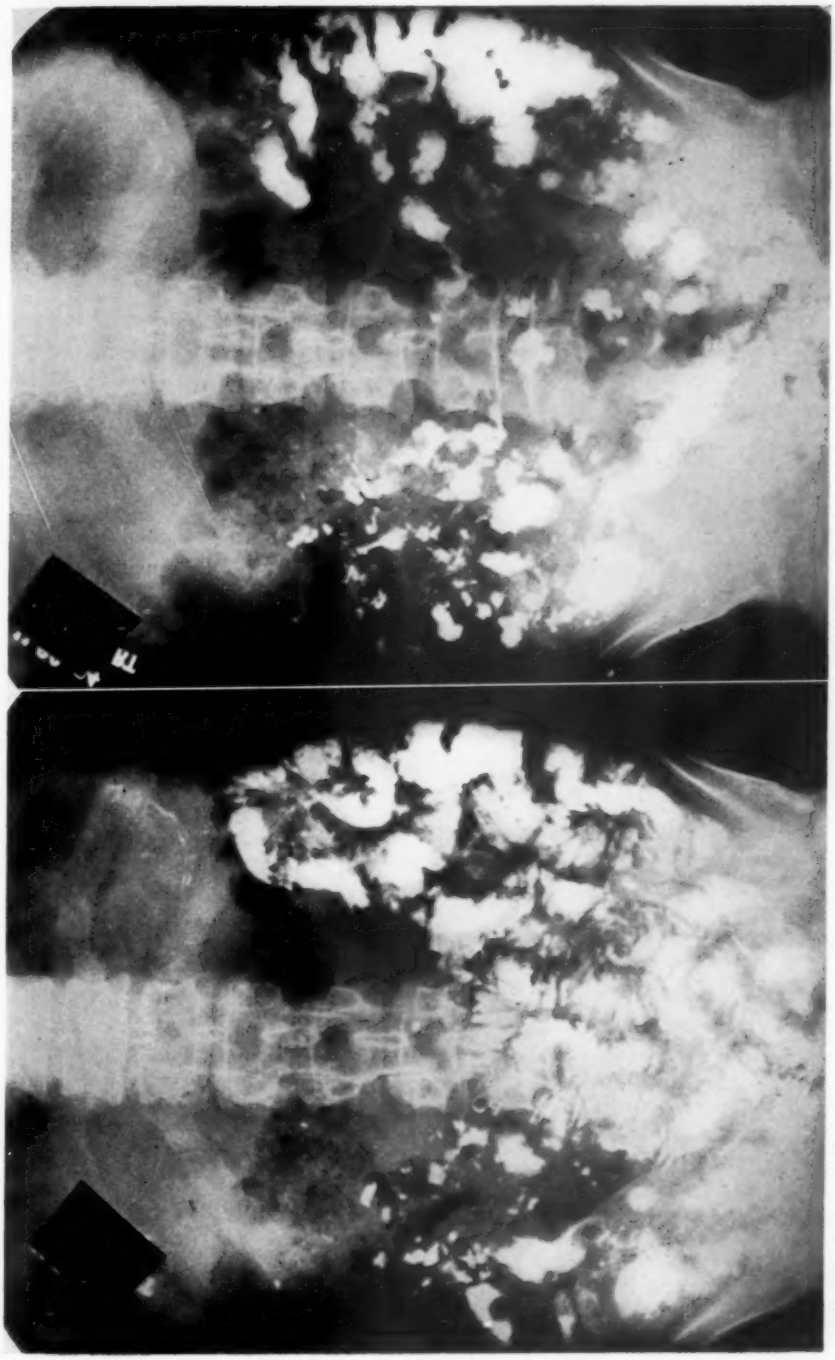

FIG. 5. Characteristic roentgenologic appearance of the small intestine during an exacerbation of sprue. The alterations in mucosal relief and clumping and pooling of barium are conspicuous.

Clinical Course of Nontropical Sprue. Tables 2 and 3 give the essential data on the clinical course in the 32 cases of nontropical sprue observed at the clinic. It has been emphasized by many writers that both the tropical and nontropical varieties of sprue are extremely chronic diseases which do not present a static picture. With the passage of time, various complicating factors have developed in the cases reported here which greatly altered the general situation. Herein appear to lie some of the characteristic features of sprue of nontropical origin. In the course of partially or badly treated nontropical sprue a host of symptoms and signs which are distinctly secondary to the original ailment may develop. Many of these have been mentioned in some detail in the preceding paragraphs.

The course of events in two cases (Cases 4 and 8) serves to illustrate this point. The details of Case 4 are given in the appendix. This patient has been under observation at the clinic for eight years and came here originally because of a chronic digestive ailment attributed to duodenal ulcer. She returned at various times with the following symptoms in this chronological order: (1) marked nutritional edema, anemia and latent tetany; (2) severe active tetany requiring parathyroid hormone for its control; (3) bone pains (osteoporosis) and hypochromic anemia, and (4) marked pellagra with glossitis. The patient in Case 8, the details of which have been mentioned by Weir and Adams in their study of fat and protein metabolism in this disease, at first responded satisfactorily to liver extract, but a relapse subsequently developed which was characterized by marked hypoproteinemia and anasarca. Neither the diarrhea nor the general systemic symptoms of the disease were satisfactorily affected by liver extract thereafter, nor was it possible to elevate the plasma protein to a normal level although a complete control of the macrocytic anemia was effected up to the time of death.

If one reviews the data in tables 2 and 3 it will be noted that in 12 of the cases (1, 2, 3, 4, 5, 8, 15, 16, 19, 20, 21, and 30), the condition was of unusually long duration, or for various other reasons one or more such "complications" as those mentioned in table 4 had developed. Six of these cases were described in my earlier report and are of the type which might be designated by some authors as "idiopathic steatorrhea" but which I would now prefer to regard as examples of prolonged or poorly treated sprue. Eighteen cases (6, 7, 9, 11, 12, 13, 14, 18, 22, 23, 24, 25, 26, 27, 28, 29, 31, 32) were of the type identical with tropical sprue in that the patients' principal symptoms were glossitis, steatorrhea, chronic digestive disturbances, malnutrition and macrocytic anemia. In certain of these cases, notably Case 24, complications of one sort or another, most often incidental to lack of adequate treatment, were beginning to enter the picture. Details of Case 24, in which the patient was a resident of Minnesota, are given in the appendix. Two additional cases (10 and 17) are more difficult to classify, the steatorrhea being relatively less conspicuous than in the other cases; in both cases skin lesions and pigmentation complicated the picture.

Upon what do these differences in the clinical syndrome depend? A variability in the ability of the mucosa of the small intestine to absorb certain essential substances may be postulated but cannot be proved. Doubtless the distinctions between the various groups are largely artificial and would be largely eliminated if longer periods of observation in individual cases were possible. The condition, as emphasized before, is a dynamic one, and for this reason sharply defined classifications are necessarily based on somewhat insecure premises.

Results of Treatment. The specific effects of liver therapy in the treatment of tropical sprue are so well established as to find a place in definitive descriptions of the disease (Hanes [18]). It is therefore of particular interest to examine the results of such treatment of sprue contracted in northern latitudes in making comparisons between the two diseases. A detailed discussion of the treatment received by the various patients in the whole series of 32 cases of nontropical sprue must of necessity be omitted. Suffice it to say that over a 10-year period the types of treatment employed were not uniform, and only in the more recently studied cases has treatment been entirely adequate. In the first group of cases reported (Cases 1 to 10, tables 2 and 3), various types of sprue diets (high in protein and low in fat) were employed, and in most of these cases calcium salts and viosterol were also given. As Linder and Harris observed, these measures alone were often productive of surprisingly good results. The use of parathyroid hormone to control tetany was necessary in two cases, but it had no apparent effect on the general course of the disease. Various salts of iron, hydrochloric acid and vitamin concentrates were employed, with little effect in some of these earlier cases. Certain of these patients were given liver extract by intramuscular injection at various times (following the suggestion of Porter and Rucker) but in only three cases (4, 8 and 10) was it used in sufficient doses or for long enough periods to ensure an optimal effect.

In the second group of 22 cases (Cases 11 to 32), liver extract was employed by oral or parenteral administration in nearly all cases. As Bloomfield and Wyckoff noted originally, whole liver or liver extract by mouth was used with some success; this was true in Case 2 of this series. The patient in Case 5 has also remained well and able to do hard work over a six-year period on liver extract taken orally. On the other hand, a number of patients have received ventriculin at various times, but almost invariably without effect. The good effects which have followed the intramuscular injection of liver extract have been noted in cases of tropical sprue by Castle and Rhoads,[10] Miller and Barker and others. Equally satisfactory responses have been noted in many of our cases, although the results have not as a whole been so uniformly gratifying as in cases of tropical sprue. Nevertheless, in at least half of this series of cases of nontropical sprue liver extract produced reticulocyte responses and rises in erythrocyte counts which were comparable to those seen in adequately treated pernicious anemia, al-

though a considerably larger dose of liver was often necessary (figure 6). Nitrogen storage was favorably affected, as was shown by studies of metabolism in Case 8 and by sharp rises in serum protein in a number of others, notably Case 31, where an increase of 2 gm. per 100 c.c. was noted over a 60-day period. Utilization of fat has also been improved, as shown by the disappearance of fat from the stools and by the control of diarrhea. I have not repeated the experiments of Barker and Rhoads concerning failure of the post-alimentary rise in blood fats in sprue and the correction of this condition by liver extract, but one would expect that the results could be duplicated in this series of cases.

The appearance of the small intestine, as shown by roentgenologic examination, has been restored to a practically normal state within relatively short periods (one to two months) by the parenteral administration of liver

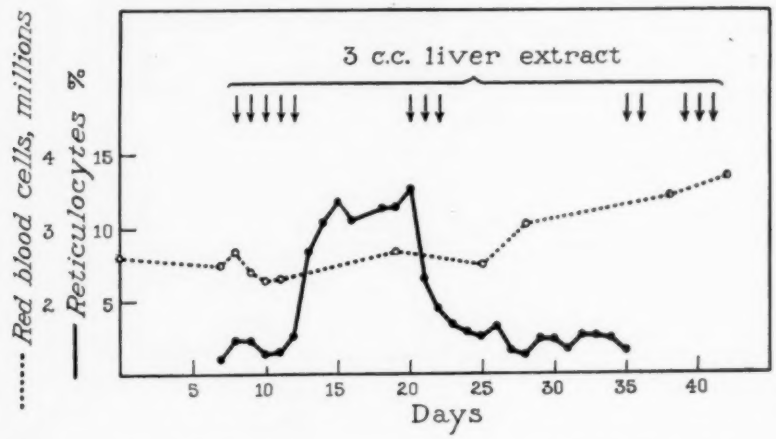

FIG. 6. Erythrocyte and reticulocyte responses to the parenteral injection of liver extract in sprue.

extract, a result which parallels exactly the observations made by Miller and Barker in tropical sprue (figure 7).

Insufficient data are available to warrant any conclusions as to the effect of liver extract on the typical "flat," glucose tolerance curve in this series of cases. All of the evidence in regard to calcium absorption and utilization is indirect; it does not appear from the clinic records, however, that liver extract of itself produced any material elevation in the level of serum calcium, although calcium is apparently stored better as fat absorption is improved. Nevertheless, calcium salts and viosterol are of obvious advantage in the treatment of patients with osteoporosis and tetany and they constitute an essential part of the treatment in such cases.

The general results of treatment in this series of 32 cases of nontropical

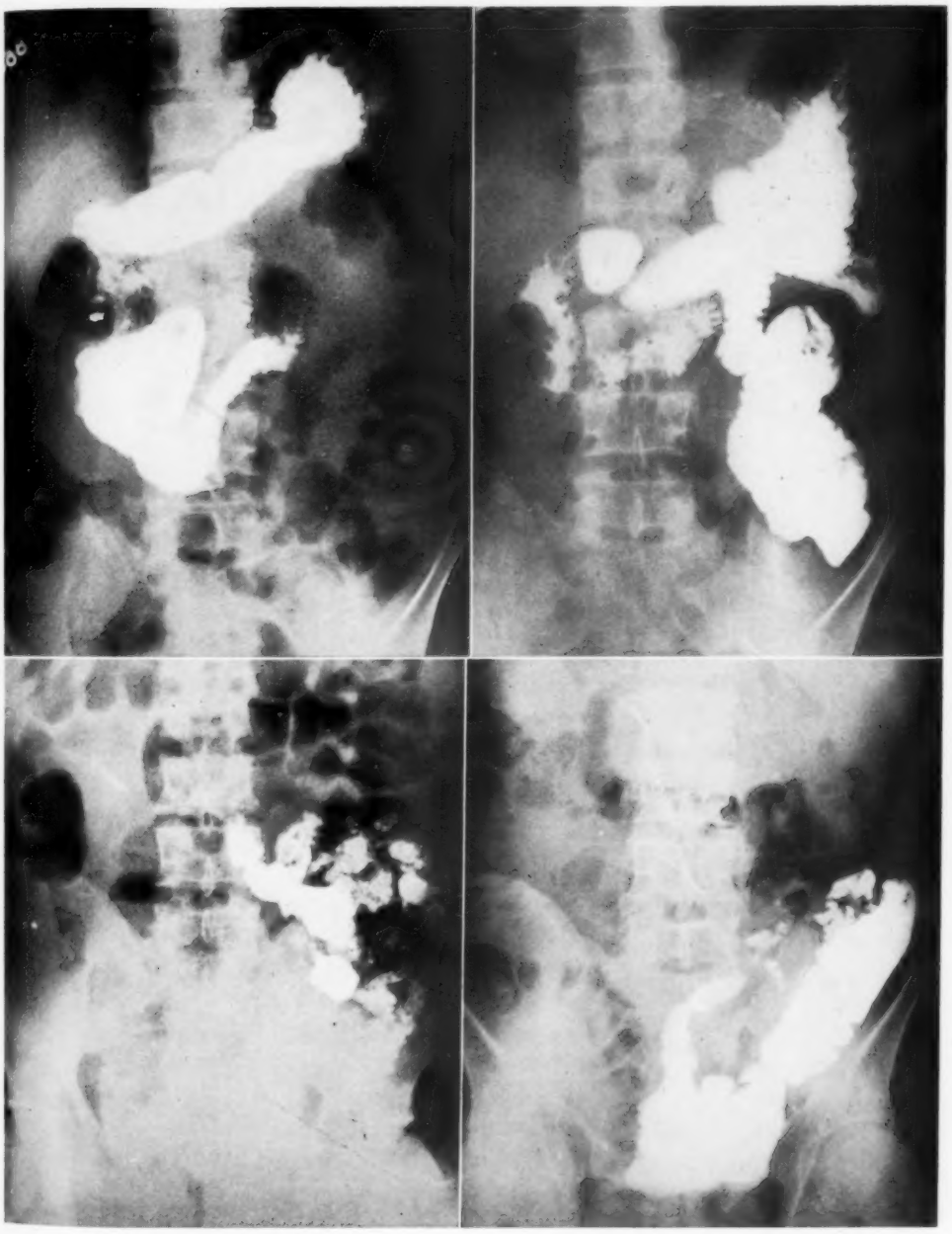

FIG. 7. Left, upper and lower. Appearance of small intestine 15 minutes and 6 hours, respectively, after the administration of barium; right, upper and lower, appearance of small intestine in same case after four months of treatment. The restoration of normal motility and reappearance of normal mucosal patterns are striking.

sprue are summarized in table 7. The preponderance of cases in which the treatment was successful is at once obvious. The failures require some comment. In Cases 1 to 10 there were four deaths, but only one of these patients (Case 8) really had prolonged and intensive liver therapy. In this case the anemia was corrected but the intestinal symptoms and hypoproteinemia continued. In the second group of 22 cases (Cases 11 to 32) there were six deaths; in three of these cases treatment with liver extract had been carried out, possibly in insufficient dosage. One of these patients (Case 30) died of a complicating disease (Landry's paralysis); a second patient (Case 29) had a complicating tuberculous, mesenteric lymphadenitis, and the third patient (Case 32) was a woman of 70 who had extensive general arteriosclerotic changes. Two patients died in relapse after discontinuing treatment with liver extract parenterally although such treatment

TABLE VII

Response to Liver Extract

Patients	Response
Living	
15	Excellent
1	Not used
3	Ineffective
1	Decreasing effect
2*	No record (old series)
22	Total
Died	
1*	Not used
6	Ineffective or partially so
2	Relapse after discontinuing treatment or inadequate treatment
1	Complicating disease
10	Total

* Old series.

had previously proved effective. The other patient who died subsequently showed only slight response to liver extract parenterally; in this case extensive bony changes (osteoporosis) and marked malnutrition were present. In certain other cases liver extract parenterally was not completely effective because of insufficient dosage; however, even in these cases there was usually some temporary or partial response to its administration.

In general the failures, either partial or complete, occurred in the group of 12 cases previously mentioned in which the condition most closely approximated the picture of "idiopathic steatorrhea," using the term here in the sense of sprue complicated by marked disturbances in calcium metabolism, hypoproteinemia and multiple vitamin deficiencies. The successes, on the other hand, were most marked in cases in which the condition most nearly resembled tropical sprue. This observation recalls the fact that infantile celiac disease does not appear to be specifically affected by liver ex-

tract. In certain of these 12 cases (notably Case 4), however, persistent treatment with large doses of liver extract parenterally eventually brought about a satisfactory remission. There was reason to suspect that in certain other cases the intestinal tract had been damaged to a point where irreversible changes had occurred, with a resulting failure of intestinal absorption.

Etiology

A discussion of the etiology of the sprue syndrome is not complete without some reference to the diseases which most closely simulate it. Fairley [11] must be credited with drawing attention to these conditions, of which the more important will be mentioned. Gastrocolic or duodenojejunocolic fistulas are of especial etiologic significance, and because of the short-circuiting of the small intestine produced by such lesions the picture of sprue may be simulated very closely. Fairley and Kilner's observations, as well as those of Mindline and Rosenheim, should be cited in this connection. We have record of one case at the clinic in which a gastrocolic fistula produced all of the usual symptoms of sprue, including macrocytic anemia, steatorrhea, nutritional edema and lowered concentration of blood calcium. Mesenteric lacteal obstruction will, as Langmead and later Fairley and Mackie have shown, simulate the sprue syndrome by cutting off the lymphatic channels through which fats are absorbed from the intestine. One of the patients referred to by them died with tetany and hypoglycemia. A patient has recently been observed at the clinic who had metastatic malignancy involving the retroperitoneal nodes, and the principal symptoms were highly suggestive of sprue.

The diseases most commonly confused with sprue, at least from the standpoint of diagnosis, are those in which destruction of the acinar tissue of the pancreas has been produced by a stone or tumor involving Wirsung's duct. In two cases in which the patients were observed at the clinic during the course of pancreatic lithiasis, sprue was closely simulated, the principal differentiating feature being the associated diabetes. One other patient with carcinoma of the pancreas presented himself at the clinic with steatorrhea, macrocytic anemia, and roentgenologic changes in the intestine which were typical of sprue. The development of obstructive jaundice shortly thereafter clarified the diagnosis of pancreatic neoplasm, which was confirmed at operation. In another case (seen in consultation, which case has recently been reported by Beard and Norris) the resemblance to sprue was very close. At necropsy a very small tumor was found blocking the pancreatic duct, with resulting pancreatic atrophy and marked fatty metamorphosis of the liver. Brems and Holst have cited somewhat similar cases which also illustrate the contributions to the clinical picture of sprue made by the steatorrhea alone. Some authors, in fact, have suggested that sprue is a manifestation of pancreatic insufficiency. The normal enzymatic activity of the duodenal contents in eight cases of this series should suffice to settle this contention.

These observations on the diseases which simulate sprue indicate certain common underlying factors and point to the relationship of failure of the absorptive function of the small intestine to the symptoms observed. The lymphatic block produced by retroperitoneal neoplasm achieves the effect of eliminating normal intestinal absorption by an indirect means. Why pancreatogenous steatorrhea will produce macrocytic anemia and sore tongue is not easily explained unless it is assumed that the presence of much undigested fat in the bowel may interfere with the absorption of certain essential portions of the vitamin B complex and the hematopoietic substance.

It has already been stated that there is much direct and indirect evidence to indicate that there is a specific failure of the absorptive function of the intestinal tract in sprue. This defect is apparently associated with, and may be caused by, some error in the absorption of the intermediary metabolism of the anti-pernicious-anemia principle or of some material with which it is closely allied. Liver extract containing this principle will, as has been demonstrated in all types of sprue, cure both the macrocytic anemia and the intestinal dysfunction.

Does the defective formation of the anti-pernicious-anemia principle, or its companion anti-sprue principle, constitute the first in a series of metabolic errors, or does small bowel dysfunction come first with failure to absorb the necessary hematopoietic principle developing secondarily? To review the large amount of evidence bearing on this question is beyond the scope of this paper. The correct and final answer is not known, but there are certain important observations bearing on the matter which must be mentioned. By feeding a modified Goldberger-Wheeler black tongue diet, a syndrome closely related to sprue may be produced in swine as well as loss of hematopoietic activity in the gastric secretions and livers of these animals (Miller and Rhoads [45]). These experiments, as Castle, Rhoads [10] and their associates [46] have noted, point to a cause sufficient to account for the secretory, and probably for the absorptive, defects in the patient with sprue. Miller and Rhoads have recently demonstrated that liver extract will produce not only functional improvement in the small bowel, but a return to its normal morphologic appearance, a fact which our experience at the clinic fully confirms. Jones and his co-workers have shown a similar improvement of the hypertrophic and atrophic gastritis associated with pernicious anemia under treatment with liver extract. One may conclude, with Miller and Rhoads, that one function of the anti-pernicious-anemia principle may be a conditioning of the functional activity of the small intestine and that this specific effect on the intestine is the one most characteristically produced in sprue.

On the foregoing basis, and following the observations of Castle, Rhoads and others,[10] a tentative explanation for the sequence of events in sprue, which is necessary for the discussion to follow, may be stated somewhat as follows: A lack of some unknown factor in diet, probably to be identified with some portion of the vitamin B complex, or a failure of the

intrinsic factor in gastric juice, may lead to failure of formation of certain products of digestion essential to the proper activities of the blood-forming organs and of the gastrointestinal tract. This deficiency, if not corrected, leads to progressive failure of the absorptive function of the small intestine; this involves a failure to absorb fat primarily, the absorption of carbohydrates and proteins being affected to a lesser degree. Deficiency in the absorption of calcium, which is closely associated with that of fat, likewise develops. Fat-soluble vitamins are poorly absorbed for the same reason; other vitamin deficiencies involving the water-soluble group are less conspicuous. With more or less complete failure in function of the small intestine continuing over a long period the complete picture of "idiopathic steatorrhea," as the term was used by Bennett, Hunter and Vaughan, with skeletal deformities, nutritional edema, tetany, cutaneous lesions and other deficiency symptoms, appears. This explanation would account for some of the distinctions which have been made between "idiopathic steatorrhea" and sprue and would agree with the observed effects of treatment in the two groups of cases mentioned in an earlier section of this paper.

Distinctions between Tropical and Nontropical Sprue

Pathologic Changes

Considerable attention has been directed toward the pathologic changes observed in fatal cases of both the tropical and nontropical varieties of sprue, and numerous reports on the matter, which are widely at variance with one another, have appeared. It is quite obvious that various types of chronic enterocolitis have been confused with sprue (Rosenthal) in certain recent reports, and that earlier investigators have been misled by postmortem changes in the intestinal mucosa. In tropical sprue, Mackie and Fairley [35] have described thinning and atrophy of the mucous membrane of the small intestine, with disappearance of the absorptive and secretory epithelium and atrophy of various organs and aplastic bone marrow. Low and Fairley cited an instance of fatal perforation of the cecum because of local thrombosis and ulceration of the thin and distended bowel. The most recent pathologic reports (Mackie and Fairley [36]) indicate that if the intestinal tract is removed and examined immediately after death, it will be found to be morphologically intact.

In nontropical sprue a variety of pathologic pictures, none of them particularly specific, have been described (Blumgart, Starr and Gardner). Lymphatic hyperplasia involving Peyer's patches and the mesenteric nodes has been mentioned, as well as submucosal edema of the digestive tract and atrophy of certain parenchymatous organs. Atrophy, dilatation, and passive congestion of the whole intestinal tract have also been described, with hemosiderosis of the liver and spleen. Lucksch and Sachs mentioned absence of the lymphatic apparatus in the small bowel, with fatty changes in the

liver. The files at the clinic contain records of three necropsies in cases of nontropical sprue. In one case (Case 30) in which the patient died of an intercurrent disease during a partial remission, the intestinal tract was entirely normal. In Case 29, reported by Mendez Ferreira and Bargen,[43] a chronic, atrophic gastro-enteritis with mucosal atrophy and edema of the submucosa were noted. A third case (32) also showed marked atrophy of the mucosa of the digestive tract, with small ulcerations which were presumably part of a terminal process (figure 8).

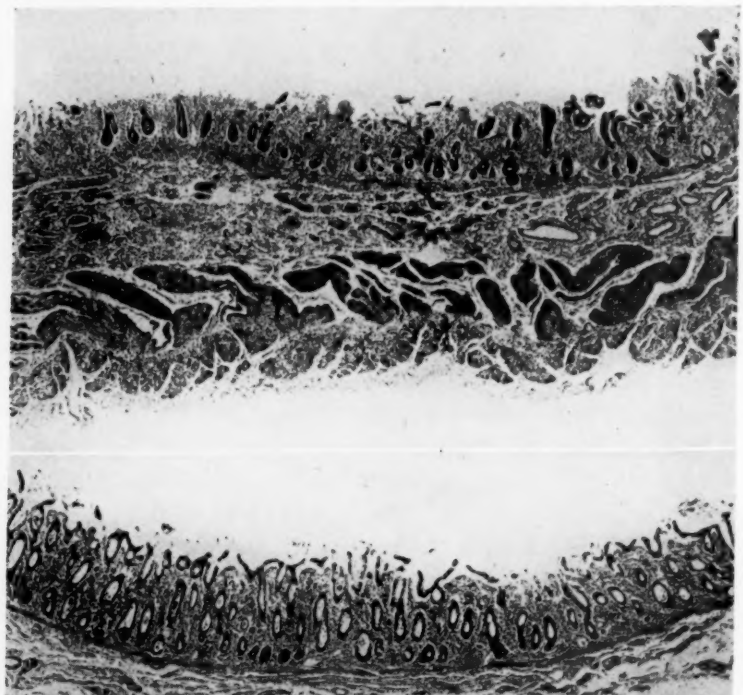

FIG. 8. Atrophy of the mucosa of the ileum in sprue (Case 32).

In short, there are no very significant differences between the pathologic picture in tropical and nontropical sprue except that, generally, the latter condition is most likely to show some definite changes in the intestinal tract. These changes, however, are neither specific nor characteristic. One must agree with Thaysen,[62] who has made an excellent summary of this matter, in his contention that the pathologic changes which have been observed in

both tropical and nontropical sprue are not significant, nor do they clearly differentiate one condition from the other.

What then are the significant differences between tropical and nontropical sprue? For reasons previously given one is forced to concede that the two types of sprue have a common basis in that a deficiency state is responsible for both. The age at which the disease makes its appearance doubtless has a definite bearing on the clinical picture, since the earlier intestinal dysfunction makes its appearance the greater the effects on growth and nutrition. The other differences in the clinical picture and response to treatment, which will be mentioned later, do not seem sufficiently great to warrant making any sharp differentiation between the two conditions. In the cases described by Bennett, Hunter and Vaughan, and in 12 of our series of 32 cases, there is much to suggest that the disease dated back to early life and in this sense may have had some relation to celiac disease. In many such cases irreversible and irreparable changes have doubtless taken place in the intestinal tract, in the skeleton, and in other viscera, and one would hardly expect specific treatment to be effective in every case.

Very active degrees of aphthous stomatitis and glossitis are apparently less common in nontropical sprue than in the tropical forms; the huge, fatty stools are also less conspicuous in sprue seen in temperate climates. Tetany and other disturbances in calcium metabolism are definitely more frequently observed in the latter group of cases. Fairley described tetany in 12 of a series of 80 cases of tropical sprue, whereas this phenomenon was noted in 9 of our 32 cases, certain of the patients having had latent tetany over long periods. Changes in the skeleton, such as osteoporosis and fracture, are said to be almost unknown in tropical sprue (Suarez); they are relatively common in the tropical form. It has been suggested that the high degree of ultraviolet radiation in the tropics may be a controlling factor in this difference. Hypoproteinemia and edema are also more frequently seen in nontropical sprue; the average figures for plasma proteins in our series of 32 cases were distinctly below those reported by Fairley for tropical sprue. Vitamin deficiencies in general are infrequently seen in tropical sprue but are common in the nontropical forms. Subacute, combined degeneration of the spinal cord has rarely been observed in tropical sprue (Giffin and others) but was noted in three cases in our series. From these facts one may assume that tropical sprue represents a milder form of intestinal dysfunction than sprue seen in temperate climates.

This may not be the only explanation, however. My personal conviction is that delay in diagnosis and failure to recognize and adequately treat the condition in its earlier stages are responsible for most of the observed variations. Both patients and physicians in the tropics where sprue is endemic are thoroughly familiar with the condition and quick to recognize it. In temperate climates, where it has long been thought that sprue was nonexistent, the diagnosis may be delayed for years, with resulting nutritional and metabolic disturbances which are almost beyond the reach of

treatment. As physicians at The Mayo Clinic have grown familiar with the sprue syndrome, the number of positive diagnoses has increased year by year and the condition is now being recognized and adequately treated before the stage of complete dysfunction has been reached. Most of the diagnoses have been made because of careful examination of stools and blood smears. As Hanes [18] has noted, a survey of old records of patients supposed to have had pernicious anemia will not infrequently reveal authentic cases of sprue; similarly, a search of cases with an indeterminate diarrhea and a poorly defined "deficiency state" will yield many examples of the sprue syndrome. If these facts are recognized, and if sprue is sought for as vigorously in northern climates as it is in the tropics, it seems certain that the artificial distinctions which have been set up between tropical and nontropical sprue will soon be regarded as unimportant.

Case Reports

Case 4. Nontropical sprue (observed over a period of eight years) with multiple complicating nutritional disturbances. A farmer's wife, who lived in Wisconsin, registered at the clinic for the first time in February 1930, being at that time 43 years of age. At a very early age she had suffered from brief episodes of diarrhea and, at the age of 16 active tetany had developed. There had then been no further attacks until she reached the age of 23, when she had suffered annual, mild attacks of active tetany occurring most frequently in March or April.

At the time of her first examination the patient's principal complaint was of right upper abdominal pain which was projected to the back; she also complained of flatulence and distress after taking fatty foods. The physical findings were not remarkable; there was no anemia and an Ewald test meal showed a free hydrochloric acid of 48 and a total acidity of 62 units. A duodenal ulcer was demonstrated roentgenologically. Because of the possibility that this duodenal lesion might be penetrating, operation was advised. At operation a large duodenal ulcer was found which had produced much contraction and obstruction on the anterior wall of the duodenum. Posterior gastro-enterostomy was performed and the patient made a satisfactory recovery.

The patient had no further trouble until August 1930, when, following a respiratory infection, anorexia and diarrhea developed. Within a few weeks marked pitting edema of the legs was noted and active tetany again developed. On examination at the clinic at this time she was found to have a definite nutritional edema with serum protein of 4.1 gm. per 100 c.c. Chvostek's and Trousseau's signs were positive and the blood calcium was 6.8 mg. Blood studies showed a moderate hypochromic anemia, the value for hemoglobin being 12.4 gm. per 100 c.c. and the erythrocytes numbering 3,750,000 per cubic millimeter of blood. The hematocrit reading was 38 per cent. No free acid could be demonstrated in the gastric contents. The stools contained much excess fat and were voluminous in spite of a very small intake of food. The value for blood cholesterol was reduced—139 mg. per 100 c.c. Roentgenologic examination of the stomach and colon showed no evidence of gastrocolic fistula. The patient made a satisfactory recovery on a high protein diet with calcium lactate and viosterol and left the hospital in good condition with the diarrhea under control and no further evidence of tetany.

The patient returned for the third time in January 1931, with a recurrence of her former symptoms. At that time she had a marked, active glossitis and had lost a good deal of weight; a considerable degree of pigmentation was also noted over

the exposed surfaces of the body. No free acid was present in the gastric content even after stimulation by histamine. The stools still contained large quantities of fat. The value for hemoglobin was 6.5 gm. per 100 c.c. and erythrocytes numbered 3,700,000 per cubic millimeter. The blood smears showed a rather marked degree of hypochromasia, but the volume index was 1.04. While the patient was under observation very active tetany developed, with generalized convulsive seizures which persisted for several days and which were extremely difficult to control. Parathyroid hormone finally brought the level of blood calcium from 6.1 to 8.2 mg. per 100 c.c., but the serum protein remained low (5.5 gm. per 100 c.c.). The diarrhea was partially controlled by a high protein diet.

In June 1931, the patient made her fourth visit to the clinic. She was still emaciated and weak, her abdomen was distended, and the blood count had remained almost unchanged. The stools still showed an excess of fat and the hypoproteinemia and edema persisted. Blood transfusions, a high carbohydrate diet with restricted fat content, calcium lactate, viosterol and yeast were the principal therapeutic measures employed, under which the patient made some gradual improvement. At this time roentgenologic examination of the stomach for the first time showed hypomotility and distention of the jejunum. The patient continued to employ the dietetic and medical measures just mentioned with fairly good results for the next four years. She was seen at the clinic annually and her only complaints were of occasional bouts of diarrhea which ceased spontaneously.

In 1935, roentgenologic examination of the small bowel showed the hypomotility and distention typical of a deficiency state and roentgenograms of the long bones showed moderate osteoporosis. The hypochromic anemia and steatorrhea persisted. At this time a series of intramuscular injections of liver extract was begun; the patient had previously taken liver and liver extract intermittently by mouth with little benefit, but the parenteral administration of liver was continued intermittently for a year, with definitely beneficial effects.

In August 1936, the patient's son was killed in an automobile accident and the attendant shock and grief brought about a profound depression with almost complete anorexia. Diarrhea also developed and the patient neglected her medications, including the liver extract. In August 1937, she registered at the clinic in very poor condition, weighing only 87 pounds (39.5 kg.). There was marked edema of the lower extremities, atrophy of the tongue, neurologic evidence of polyneuritis and a marked pellagrous eruption over the lower extremities, neck and hands. Laboratory examinations were carried out following hospitalization. Urinalysis gave negative results. The hypochromic anemia persisted, the value for hemoglobin being 6 gm. per 100 c.c. and erythrocytes numbering 3,200,000 and leukocytes 4,400 per cubic millimeter. The blood calcium and phosphorus readings were, respectively, 7 and 4 mg. per 100 c.c. Undried stools contained about 18 per cent of solid fat by weight, of which about two-thirds was in the form of fatty acids. The serum protein was 4.6 mg. A glucose tolerance test taken after a brief period of treatment gave an essentially normal curve. Roentgenograms of the thorax and long bones were negative; those of the small intestine showed hypomotility but nothing else of significance. Roentgenologic examination of the colon again was made to exclude gastrocolic fistula, with negative results. Treatment with a high protein diet, large doses of brewers' yeast and liver extract parenterally resulted in slow but satisfactory improvement. At the time of her dismissal, five weeks later, the patient was taking a 3,000 calorie diet with little difficulty, but it was still necessary for her to restrict the fat content somewhat in order to avoid diarrhea. The serum protein had risen to 6 gm. per 100 c.c. and the blood calcium to 8.6 mg. The pellagrous eruptions and the nutritional edema had entirely disappeared. Moderate hypochromic anemia still persisted; the value for hemoglobin was 9.0 gm. and erythrocytes numbered 4,000,000.

The patient has progressed very well during the past year on a continuation of this same form of treatment and is in reasonably good condition at the present. She receives two injections of liver extract, each equivalent to 100 gm. of fresh liver, weekly. Her weight and strength are well maintained and no symptoms of sprue have been noted.

Case 24. The syndrome of "tropical" sprue in a native of Minnesota. A farmer residing in southern Minnesota, aged 41 years, registered at the clinic in March 1934. For the previous three years he had suffered from diarrhea for about six weeks out of each year, the attacks usually occurring during the autumn months. Flatulent indigestion and anorexia had been noted more or less continuously for about the same period. With the most recent attack of diarrhea he had suffered from paresthesias and cramps in his extremities, their description being very suggestive of tetany. He had lost about 30 pounds (13.6 kg.) and there had been a corresponding loss in strength. He said that he had not noted a sore tongue up to the time of his final examination.

On physical examination the patient was weak, undernourished and dehydrated. His tongue had a smooth, atrophic appearance but was otherwise normal. There was some pigmentation of the exposed surfaces of the body and clubbing of the fingers and toes was noted. Chvostek's and Trousseau's signs were negative. The abdomen was moderately distended with gas; no organs or masses could be felt. Neurologic examination showed no evidence of changes in the central nervous system. Laboratory examinations gave essentially negative results except for showing rather marked anemia. The value for hemoglobin was 10.8 gm. per 100 c.c. and erythrocytes numbered 2,860,000 and leukocytes 8,400 per cubic millimeter. The serum calcium was 8.9 mg. The morphologic appearance of the blood smears was very suggestive of pernicious anemia; an Ewald test meal showed free hydrochloric acid of 40 and total acidity of 54 units. The stools were not conspicuously fatty at the time of this first examination; however, a tentative diagnosis of sprue was made and treatment with whole liver by mouth was begun.

The patient returned to the clinic two months later. In the interval he recalled that there had been one earlier attack of glossitis which he had not remembered when first questioned about the matter. At the time of his second examination he was somewhat improved, although he still suffered occasionally from diarrhea and his appetite was still poor. His blood, however, was approximately normal, the value for hemoglobin being 16 gm. per 100 c.c. and erythrocytes numbering 5,240,000 and leukocytes 9,100 per cubic millimeter. Stained smears showed no significant abnormalities.

In February 1937, the patient again returned to the clinic. He had been quite well during the preceding year and had regained the weight which had been lost prior to his first examination. About a month prior to this registration, however, profuse diarrhea had developed and he had again lost about 30 pounds. He complained greatly of abdominal flatulence, cramps and marked anorexia. Physical examination gave essentially the same results as in 1934 except for increased distention of the abdomen. The stools were found to contain large amounts of fat and were offensive, yellow, foamy and voluminous. The blood counts were not remarkable; the value for hemoglobin was 14 gm. and erythrocytes numbered 4,000,000 and leukocytes 4,900. Morphologic study of the stained blood smears, however, showed typical macrocytosis. The serum calcium was 8.1 mg., phosphorus 2.1 mg., protein 5.5 gm. and cholesterol 150 mg. per 100 c.c. Roentgenograms of the small bowel showed the dilatation, hypomotility and irregularities of the mucosal pattern that are commonly seen in sprue. Definite osteoporosis of the spine and pelvic bones was also noted. Free hydrochloric acid was still present in the stomach; the test showed values of 10 units after an Ewald meal.

Because of the cachexia and severe diarrhea the patient was at once hospitalized for treatment. Liver extract in amounts containing the active principle from 100 gm. of fresh liver was injected daily for one week. Striking clinical improvement was noted at once. The diarrhea was checked, the patient's appetite returned, and there was a rapid gain in weight and strength. At reëxamination six months later the blood was entirely normal, both in respect to the cell counts and morphologic appearance of stained smears; the blood calcium and phosphorus had returned to normal levels and the serum proteins had increased to 6.3 gm. per 100 c.c. Roentgenologic examination of the intestinal tract showed definite improvement in the appearance of the bowel; however, there were still some abnormalities in the ileum and lower portion of jejunum. The osteoporosis was less marked than before.

Apparently the use of liver by mouth had induced a remission which lasted in this case for almost two years. The patient had also taken extralin and hydrochloric acid at various times, but the relapse which brought him to the clinic in 1937 had developed in spite of all these measures. The rapid and complete response of all of the symptoms and signs of sprue to treatment with liver extract parenterally was very striking.

Summary and Conclusions *

A series of 32 cases of the sprue syndrome encountered in residents of temperate climates is reviewed and compared with examples of tropical

* Since this article was submitted for publication a number of reports on the nature and treatment of nontropical sprue have appeared in the literature. Their importance warrants brief reference here. Brull and his collaborators [Brull, Lucien, Lambrechts, A., and Barac, G.: Sprue nontropicale. Étude approfondie de quatre cas observes en Belgique, Rev. Belge des Sci. Med., 1938, x, 457–532], in reporting an extensive metabolic study of four cases of the disease, have been impressed by the favorable effect on steatorrhea which followed the administration of vitamin B_2 (riboflavin) in two cases; they agreed that this observation needs further confirmation, but they pointed out that this phenomenon must be regarded as evidence favoring the idea that the fundamental feature of steatorrhea may depend on B_2 avitaminosis.

Bassett and his coworkers [Bassett, S. H., Keutmann, E. H., van Zile Hyde, H., Van Alstine, H. E., and Russ, E.: Metabolism in idiopathic steatorrhea. I. The influence of dietary and other factors on lipid and mineral balance, Jr. Clin. Invest., 1939, xviii, 101–121], [Bassett, S. H., Keutmann, E. H., van Zile Hyde, H. and Van Alstine, H. E.: Metabolism in idiopathic steatorrhea. II. Effect of liver extract and vitamin D on calcium, phosphorus, nitrogen and lipid balances, Jr. Clin. Invest., 1939, xviii, 121–135], have likewise reported the results of their metabolic studies on four patients with "idiopathic steatorrhea"; in these cases striking calcium deficiencies and osteoporosis were present. Prolonged parenteral administration of liver extract to these patients failed to cause improvement in the absorption of fatty acids, calcium, phosphorus or nitrogen. These findings are in general accord with experience at the clinic in the treatment of patients presenting marked mineral and vitamin deficiencies, who were, as a rule, refractory to liver therapy.

Hotz and Rohr [Hotz, H. W., and Rohr, K.: Die einheimische Sprue (Auf Grund von 22 eigenen Fällen), Ergebn. d. inn. Med. u. Kinderh., 1938, liv, 174–268], in a comprehensive review of 22 personally observed cases of "einheimische Sprue" in Switzerland, gave an enthusiastic report on the general effects of liver therapy but did not check the effect on excretion of fat by metabolic studies. The gains in weight reported by them, however, compare with those noted in the clinic series; such rapid increases can hardly be interpreted as having occurred on any basis other than an improved capacity for intestinal absorption of foodstuffs generally.

Fanconi [Fanconi, G.: Zöliakie, Deutsch. med. Wchnschr., 1938, lxiv, 1565–1568] and also Engel [Engel, Rudolf: Sprue und Vitamine-K-Mangel, Med. Welt, No. 4, 1939], both have called attention to the probable defect of intestinal absorption in respect to the fat-soluble antihemorrhagic vitamin K and the relation of this defect to the hemorrhagic features which may characterize the disease.

sprue and with certain cases which have been classified as examples of "chronic idiopathic steatorrhea."

Twenty of the 32 patients presented symptoms and signs which were virtually identical with those seen in tropical sprue; these patients responded in a specific manner to liver extract. The remaining 12 patients presented various metabolic and nutritional disturbances, including tetany, osteoporosis, hypoproteinemia and various vitamin deficiencies. The condition in these cases was identical in all respects to that described in the English and Scandinavian literature as "idiopathic steatorrhea." The response to liver extract in these cases was often unsatisfactory, but in certain cases in which the patients were adequately treated, good results were obtained.

No fundamental difference between these two groups of cases was demonstrable, although it was apparent that intestinal dysfunction was more marked, or at least affected the absorption of more substances, in the smaller group of patients.

Distinctions among tropical sprue, nontropical sprue and idiopathic steatorrhea are largely artificial, the more intractable nature of the condition in the group of cases described under the last-mentioned caption being largely a matter of late diagnosis and inadequate treatment.

The sprue syndrome is not uncommon in temperate climates, and its earlier recognition and treatment would largely eliminate the late "complicated" cases.

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GOLD THERAPY IN ARTHRITIS; OBSERVATIONS ON 100 CASES TREATED WITH GOLD SODIUM THIOSULPHATE AND AUROCEIN *

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Our interest in gold salts as a means of treating rheumatoid and osteo-arthritis was stimulated by the work of Dr. Jacques Forestier, who in 1934 published [1a] the results of his observations on 500 cases of rheumatoid arthritis, treated over a period of five years. He stated that it had previously been demonstrated by Mollgaard that injections of gold salts would arrest the progress of tuberculosis. It was rational, therefore, that the same remedy might be of service in other chronic diseases of infective origin. Forestier [1b] claimed that 70 to 80 per cent of the arthritic patients treated by him responded well to gold salt therapy.

In 1936, approximately nine years after he first introduced gold therapy in the treatment of arthritis in Europe, Forestier reviewed his experience with this type of treatment and reported [1c] that in chronic progressive rheumatoid polyarthritis the advance of the disease can be arrested by gold therapy in 85 per cent of the cases.

In 1937 Hartfall and Garland [2] reviewed 900 cases of chronic arthritis treated over a period of five years with gold salts. This was the largest series of cases reported up to that time. They obtained clinical improvement in approximately 80 per cent of the cases of rheumatoid arthritis and in more than 50 per cent of the cases of osteo-arthritis. The beneficial clinical results in the latter group were not comparable in degree, however, to those obtained in the rheumatoid group. Hartfall and Garland's [2] clinical observations have been confirmed by other European workers. Gerald Slot,[3] Pemberton,[4] Baker,[5] Crosby,[6] Buckley,[7] Sostberg, Schade, Steuber and Warburg [8] have all reported approximately the same results.

In the American literature only scant reference to gold therapy has appeared to date. Sashin and Spanbock [9] reported on 22 selected cases of active rheumatoid arthritis which they treated with gold salts intravenously with good results. Brief reports by Oren [10] and by Phillips [11] have appeared. Oren [10] reported on a series of 100 cases of various forms of arthritis. Of the 66 cases of atrophic arthritis in the series, 60 responded very well to the gold salt therapy. Twelve cases of gonorrheal arthritis all did exceedingly well. Of the 22 cases of hypertrophic arthritis, 13 cases improved under treatment. Phillips [11] treated 20 cases, nine of whom had atrophic or rheumatoid arthritis, eight hypertrophic or osteo-arthritis, two peripheral neuritis, and one subdeltoid bursitis. He used the technic advocated by Forestier.

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Only six of the 20 cases showed any subjective improvement and he consequently discontinued this form of treatment. Toxic reactions in his cases were numerous. Tegner [12] writes, " European workers feel that up to date, gold salt therapy has not had a fair trial in the United States."

The American Committee on Rheumatism [13] is becoming more and more impressed by the number of favorable European reports on gold salt therapy (chrysotherapy) in arthritis. The American Committee is still uncertain, however, of the value of gold salts in arthritis and of the proper indications for their use. Hench [14] for example, writes, " Apparently definite benefit results from such therapy in an impressive number of cases, but until more controls are set up, we will not know the exact value of the method and how fully justified one is to run the risk of frequent and rather serious toxic reactions." Later, in the same review, he states, " Among the pitfalls in a study of therapy, is that of a dangerous but helpful drug; its full effect must be studied carefully, for what seems to be a dangerous drug today (e.g., gold) may be improved by further knowledge."

It is pertinent to observe at this point that there has been no uniformity among different investigators in the preparation of gold employed, the route of administration, the size of dose and number of doses per series, the number of series required, and the extent of adjuvant therapy during courses of treatment with gold.

Forestier himself [1] used several preparations, including myochrysine (sodium aurothiomalate), allochrysine (sodium aurothiopropanol sulfonate) and myoral (calcium aurothioglycolate). Hartfall and Garland [2] used myochrysine, crisalbine (sodium aurothiosulfate), and solgonal B (aurothioglucose). Oren [10] employed Aurocein which he describes as a solution of sulfhydryl gold napthyl trisulpho-carbonium derivative. Phillips [11] used myochrysine. The reasons for using the different preparations of gold are obscure, and appear to have been dictated by availability of the particular preparation, or by the desire to find one which is therapeutically effective and at the same time not toxic.

The mode of administration has also varied. The intramuscular route is preferred by some over the intravenous route because of ease of administration and gradual absorption of the drug. In general, the intravenous preparations, such as sanochrysin, contain approximately 40 per cent of metallic gold, whereas the intramuscular preparations, such as myochrysine, contain approximately 50 per cent of metallic gold. The mode of injection seems to have had little effect on either the therapeutic results or on the toxic reactions which sometimes have occurred.

Differences of opinion exist as to what should constitute the size of the initial dose, the number of doses and total dosage per series, and the number of series required. In regard to the initial dose, the general tendency has been downward. In their early work the European investigators gave from 200 to 500 milligrams, but because of the numerous toxic reactions which developed, the initial dose was more or less universally reduced to 50 milli-

grams. In the last three years the tendency has been to go even lower, and to start with 5 or 10 milligrams.

In regard to the total dose per series, opinion ranges from one gram (Hartfall and Garland,[2]) to 2.5 grams (Bach[15]). It would be futile to compare one set of figures with another, as there is such variability from worker to worker in the preparation of gold used, the mode of administration, and frequency of injections and the type of patients studied.

Rest periods between series of injections vary from four to eight weeks (Forestier and Bach), to two to three months (Hartfall and Garland and Buckley) to six months (Baker).

Relapses of arthritic symptoms are not uncommon after the first course. They seldom occur after the second course of treatment in patients who respond favorably. The most usual time for the appearance of relapses is about six weeks after the completion of the first course. Forestier[1] consequently advises beginning the second course of treatment one month after completion of the first. Hartfall and Garland,[2] on the other hand, believe that the interval between completion of the first course and commencement of the second should be at least two to three months, in order to avoid the possibility of injecting additional gold salts into a patient who may be on the verge of a delayed toxic reaction.

Recurrence of arthritic symptoms should never discourage the physician from giving a second series of injections. The experience of many workers[2] has been that, while one series may fail to benefit or completely relieve the patient with rheumatoid arthritis, the second series is often followed by complete and permanent relief.

All European workers[2] agree that, despite the greatest care in the administration of gold, toxic reactions are encountered in 40 to 50 per cent of the cases. The most common toxic manifestations are cutaneous irritations (particularly pruritus) and gastrointestinal upsets. These mild reactions are relatively unimportant and clear up within a few days or weeks. About 15 per cent, however, manifest more severe reactions, such as generalized exfoliative dermatitis, severe gastrointestinal disturbances, jaundice and even aplastic anemia. These severe toxic reactions may last for a year or longer and may even prove fatal.

Jaundice developed in 9.4 per cent of Hartfall and Garland's[2] cases. They pointed out, however, that this high percentage should not be regarded as the ordinary incidence of toxic jaundice following gold therapy because two patients in their clinic who were not on gold therapy developed jaundice coincidently, and that there was a mild epidemic of infectious jaundice in that region from which most of their cases were drawn. It is interesting to note that most of their cases treated with gold salts which developed jaundice became worse during that period. This is in direct contrast with the experience of Wyatt and Thompson,[16] who purposely produced jaundice in 10 cases of rheumatoid arthritis by administering relatively large doses of bile salts and bilirubin intravenously. They stated that this combination

had an ameliorating effect on the symptoms of atrophic arthritis. Hench [14] has also noted that patients with rheumatoid arthritis treated at the Mayo Clinic were completely free of arthritic symptoms during the period that they suffered from jaundice, and that their arthritic symptoms usually reappeared following the disappearance of the jaundice.

The mechanism responsible for the toxic reactions in gold therapy is unknown. In animals approximately 80 per cent of the gold is excreted in the first 24 hours and the remaining 20 per cent is deposited in the mesenchymal tissues.[2] Toxic reactions may be due to hypersensitivity of patients to even minimal doses, or to accumulation of gold in the tissues beyond a critical level.

The mode of the therapeutic action of gold in arthritis is likewise unknown. In this respect its empirical use may be likened to the employment of arsenic and mercury in syphilis. Forestier and Certonciny [1] believe gold has no direct effect on the etiológic factor in arthritis, but that it checks the progressive inflammatory changes in the joints. At least part of the beneficial effects may be due to what, for want of a better term, is called "shock therapy." The writers have repeatedly seen in their own practice instances in which a slight overdose of gold produced a reaction similar to a foreign protein reaction, accompanied by chills, fever and leukocytosis. It is probable, however, that an additional factor is present, since patients who have previously shown no improvement on vaccine therapy respond to gold. In this connection, it is interesting to note that Yanagisawa and Kawai [17] point out that the only gold compounds which produce beneficial results are those which contain sulphur. In the treatment of experimental tuberculosis in guinea pigs they found that one of their gold salt compounds was just as effective when the gold radicle was removed and the sulphur radicle left in.

To determine this point, we have analyzed 50 milligrams of gold sodium thiosulphate and found that it contains 12.5 milligrams of sulphur. It seems to the authors, from their experience in giving sulphur therapy, that it is questionable if this small dose of sulphur, given once a week, could have any beneficial effect on the arthritic patient.

To date there is not available a method for determining hypersensitivity to gold. The intravenous use of vitamin C or calcium gluconate has not proved of help in preventing or neutralizing toxic reactions. When reactions do occur, there is no known method for shortening the attack except by ceasing treatment with the drug until all evidence of toxicity has disappeared.

After a study of the available literature on gold salt therapy in arthritis, the present writers began to use this form of therapy at the Arthritis Clinic of the Hospital for the Ruptured and Crippled. The cases chosen were those that had proved to be refractory to all other accepted methods of treatment. We believe that this is the best way to set up a control series to test the relative efficacy of any new form of treatment.

In our series, the following precautions were taken routinely in an effort to avoid needless toxic reactions:

1. Hypersensitive patients or patients with any history of skin, liver, kidney or intestinal irritability were eliminated from this study.

2. Before beginning treatment, each patient had a complete blood count, urinalysis and determination of his sedimentation rate. During treatment, frequent examinations of the patients' urine were carried out, and if any specimen showed the presence of albumin or urobilinogen, where previously the urine had been negative, treatment was usually discontinued until the urine became normal again. In some cases, we found that the presence of albumin in the urine was not a contraindication to further treatment if given cautiously. Blood counts and sedimentation rate studies were also carried out at frequent intervals during the course of treatment.

3. Each patient thoroughly understood the possibilities of failure as well as the possibilities of toxic reactions before treatment was instituted.

4. The gold salts solution was prepared freshly by dissolving the powdered salt in 5 c.c. of triple distilled sterile water immediately before injection. The solution was injected slowly. All injections were administered by one physician. The clinical results of treatment, however, were observed and estimated by the three authors after personal recall interviews with each patient.

5. The intravenous method of administration was used because we thought it was easier to observe the immediate results. In those cases which presented technical difficulties, Aurocein was used intramuscularly. This preparation contains a 5 per cent solution of sulfhydryl gold napthyl trisulpho-carbonium derivative and comes in 2 c.c. ampules. A series consisted of two injections a week for six weeks, making a total of 12 injections per series, with an interval of one month or six weeks between series. If any toxic reactions appeared we discontinued the injections immediately and did not renew the medication until all symptoms of toxicity had subsided. In subsequent treatments, we lengthened the interval by giving one ampule a week.

6. We preferred to use gold sodium thiosulphate because it was the salt originally used by Mollgaard in 1924. It has been used extensively with success in lupus erythematosis and in arthritis over a period of 14 years, and its relative toxicity has been fairly well established. Further advantages of the Abbott gold sodium thiosulphate used in this series are that it is an American product, is easily obtainable and it has been approved by the Council on Pharmacy and Chemistry of the American Medical Association. Moreover, Forestier [1] pointed out that gold sodium thiosulphate was apparently less toxic, although slightly less efficient than the other commonly used gold salts.

7. Dosage: The initial dose of gold sodium thiosulphate was 5 milligrams. If no toxic reactions developed, the dose was increased by 5 milli-

grams and then by larger amounts according to the schedule found below:

1. 5 mg.	5. 50 mg.	9. 100 mg.	13. 100 mg.
2. 10 mg.	6. 75 mg.	10. 100 mg.	14. 100 mg.
3. 15 mg.	7. 100 mg.	11. 100 mg.	Total 990 mg.
4. 35 mg.	8. 100 mg.	12. 100 mg.	to each series.

As can be seen, the highest dose given was usually 100 milligrams. In only one case did we go up to 125 milligrams. The total dosage in a series exceeded 1000 milligrams in only one case. A series usually consisted of 12 to 15 injections and rest periods were from six to eight weeks. Two series of injections were given to those patients who could tolerate the treatment. However, there is no contraindication to giving additional series, up to five series, if the preceding treatment does not entirely cure the patient, provided the interval between series is lengthened by at least one month between series.

To the extent that chronic arthritis cases can be classified clinically, the 100 cases consisted of a group of 50 with rheumatoid arthritis, of 20 with osteo-arthritis and of 30 with a mixed form of arthritis. The criteria for evaluating the results in this study after gold therapy were as follows:

Excellent results: Complete cessation of all subjective symptoms, disappearance of swelling, return to normal range of movement, ability to sleep and to return to gainful occupation.

Good results: Diminution of pain and swelling and increased motion of involved joints.

Fair results: Diminution of pain or swelling or lessening of restriction of joint motion.

Poor results: No change or improvement.

The results obtained in the 100 cases of chronic arthritis are shown in table 1.

TABLE I

	Rheumatoid cases	Osteo cases	Mixed cases
Number of Cases	50	20	30
RESULTS:			
Excellent results	1	none	1
Good results	5	4	0
Fair results	18	5	7
Poor results	26	11	22

In the rheumatoid group therefore, 24 out of 50, or 48 per cent of the patients showed some degree of clinical improvement. In the osteo-arthritic group, nine out of 20, or 45 per cent showed improvement, while in the mixed group, eight out of 30 patients, or 26 per cent improved. Of the entire group therefore, 41 per cent showed some degree of clinical improvement following gold salt therapy. This is a definite and substantial

percentage of improvement in cases that did not respond satisfactorily to other accepted forms of arthritic therapy.

Forestier [1] and Hartfall and Garland [2] emphasized that the efficacy of gold therapy in chronic arthritis is in inverse ratio to the duration of the disease. We classified our cases into two groups: those who had the disease for less than two years, and those who had been ill for two years or longer (tables 2 and 3.) In the group that gave a history of less than two years' duration, there were 14 rheumatoid, seven mixed and five osteo-arthritic cases. In the group of over two years' duration, there were 36 rheumatoid, 23 mixed and 15 osteo-arthritic cases. In the group that gave a history of

TABLE II

Clinical Results Following Gold Therapy in Arthritis Cases of Less Than Two Years' Duration

	Rheumatoid cases	Mixed cases	Osteo cases
Number of Cases	14	7	5
RESULTS:			
Excellent results	0	1	0
Good results	1	0	2
Fair results	8	1	1
No change	5	5	2

TABLE III

Clinical Results Following Gold Therapy in Arthritis Cases of More Than Two Years' Duration

	Rheumatoid cases	Mixed cases	Osteo cases
Number of Cases	36	23	15
RESULTS:			
Excellent results	1	0	0
Good results	2	0	2
Fair results	13	6	4
No change	20	17	9

less than two years' duration, 54 per cent of the cases improved in some degree. In the group of patients who had the disease for over two years, only 38 per cent showed improvement. Our results therefore, are in agreement with those of previous workers.

One sees statements in the literature [1, 2, 12] that gold therapy is more effective in patients of the early and middle age groups than in those of the latter decades of life. We have classified the patients in this study under separate age groups: 20–40 years; 40–50 years; 50–60 years; and 60 years and over. The results in these age groups are summarized in the following table:

TABLE IV

Results of Gold Therapy in Arthritis According to Age Groups

	Rheumatoid cases	Mixed cases	Osteo cases
Age 20–40	19	6	4
RESULTS:			
Excellent results	0	0	0
Good results	2	0	1
Fair results	7	1	0
No change	10	5	3
Age 40–50	16	11	3
RESULTS:			
Excellent results	0	1	0
Good results	1	0	1
Fair results	7	4	0
No change	8	6	2
Age 50–60	10	9	9
RESULTS:			
Excellent results	0	0	0
Good results	2	0	2
Fair results	4	2	2
No change	4	7	6
Age 60 or over	5	4	4
RESULTS:			
Excellent results	1	0	0
Good results	0	0	0
Fair results	2	1	3
No change	2	3	1

From these statistics, it is evident that improvement in the age group 20 to 40 occurred in over 37 per cent of the cases, while in the age group of 40 and over, improvement occurred in over 45 per cent of the cases. Our results, therefore, are at variance with previously published statistics and indicate that advancing age is no contraindication as to the use of gold therapy.

The sedimentation rate of red blood cells did not always prove to be, in our experience, a reliable index for judging clinical progress. For example, in the improved group of cases where one would ordinarily expect a lowered sedimentation rate, 47 per cent of the cases showed an elevated sedimentation rate at the end of the period of treatment. On the other hand, in those cases in which no clinical improvement occurred, we found that in 80 per cent of the cases the sedimentation rates showed a lowered level at the end of treatment. This series has only been carried on over a two year period. Over a longer period of observation these figures will perhaps change and our experience may conform with the experience of European workers.

Toxic reactions were observed in 17 patients. In 11, dermatological lesions formed the outstanding symptoms. These were in the nature of localized or generalized rashes, which persisted generally from three days to a week. In one case, the skin rash lasted two and one-half months. This

patient emphasized to us the latent danger of administering gold therapy since he had had only two intravenous injections of gold sodium thiosulphate (sanochrysin) which were given a week apart. He received 10 milligrams at the first injection and 20 milligrams at the second injection. The rash appeared immediately after the second dose. There were also four cases with gastrointestinal disturbances characterized chiefly by nausea and anorexia. These symptoms, however, cleared up promptly. Edema of the hands and feet occurred in two cases. In a third case, the development of edema proved to be alarming because it involved the glottis. This patient was delirious for three days, had increasing dyspnea and had to be relieved finally by tracheotomy. This patient also had had only two intravenous doses, a total of 30 milligrams of gold sodium thiosulphate. After recovery from the toxic reaction, this patient who had rheumatoid arthritis has now been completely free of all arthritic symptoms for a period of one year. There have been no fatalities.

Summary

In this series, we have attempted to determine the therapeutic effects of gold salts in the treatment of arthritis, as well as their limits of safety. Our observations warrant the following statements:

1. Gold may be given as gold sodium thiosulphate (sanochrysin) intravenously, or sulphydryl gold napthyl trisulpho-carbonium (Aurocein) intramuscularly, without serious permanent injury in the great majority of patients, if reasonable precautions are observed. These precautions include careful selection of patients, small initial doses and gradual increase in dosage, and constant vigilance for evidences of toxicity.

2. In the rheumatoid group, 24 out of 50 patients (48 per cent) showed definite clinical improvement according to our criteria. In the osteo-arthritic group, nine of 20 patients (45 per cent) improved, while in the mixed group, eight of 22 patients (26 per cent) showed improvement. Of the entire group therefore, 41 per cent showed some degree of clinical improvement following gold salt therapy. The criteria for improvement are discussed. Our percentages of successful results in cases refractory to usual methods of treatment were not as good as those reported by European workers, but their series included early and untreated cases of arthritis, many of which might have been cured by other methods of treatment.

3. We feel that our clinical results would have been better had larger doses been employed, or had we used one of the stronger salts, but toxic reactions would have been more numerous and more alarming.

4. In the present status of our knowledge, gold salt therapy appears to be too dangerous for general use. It should be undertaken only when the case is refractory to the usual forms of treatment. The risk involved should be explained to the patient before treatment is instituted.

5. There is no standard procedure for the administration of gold salts.

Increasing experience may lead to a standardized therapeutic procedure. The mode of action of gold salts and their optimal dosages require further investigation.

6. In our series, the percentage of toxic reactions was only 17 per cent. The majority of these manifestations were mild in degree. Three cases in whom more serious reactions occurred, eventually showed improvement in their arthritic symptoms.

7. At the present time, we have 200 cases under treatment. This group will be enlarged and we hope to submit a further report at the end of five years.

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RIGHTWARD DEVIATION OF THE AXIS OF THE T-WAVE AS AN INDEX OF MYOCARDIAL DISEASE *

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The clinical significance of the height of the T-wave in Leads I and/or III of the electrocardiogram has been approached from different angles by different authors. Eideiken and Wolferth [1] studied low T_1, low T_1 and T_2, and low T_2 with inverted T_3. They point out that a T_1 less than 2 mm. in height is usually associated with myocardial disease unless the position of the heart is vertical. In the latter case the non-significant low T_1 is generally associated with a low R_1. These authors do not consider the electrical axis of the T-wave except as far as the changes in amplitude in the several leads may reflect axis changes. In the course of a study of left axis deviation, Proger and Minnich [2] emphasize three signs which accentuate the abnormality of the picture. These are low T-waves in Lead I, high T-waves in Lead III, and deep S-waves in Lead II.

As a result of observations made by us during the past several years, we have become convinced that the electrical axis of the T-wave is of more significance than mere lowness or highness of a T-wave expressed in millimeters. For example, an upright T_1 of 1 mm., even when R_1 exceeds 6 mm. in height, is not necessarily significant when all the T-waves are low. It consequently appears desirable to attempt a more general formulation of the problem expressible in quantitative terms, but simple enough to be practicable for routine use. The latter requirement today rules out the method employed by Wilson, Macleod, Barker and Johnston [3] which depends upon the determination, by use of a planimeter, of the net positive or negative areas of the QRS complexes and of the T-waves.

The method of analysis herein described is an outgrowth of observations made several years ago (Ashman and Hull,[4] page 89). We found, from an analysis of the electrocardiograms of 100 normal adults, that while T_1 was either higher or lower than T_3 when the average electrical axis of the QRS complex lay to the right of about $+ 30°$, the T_1 was always higher than T_3 when there was a left axis deviation, with an exception to be noted below. Since that time we have watched the T_1/T_3 ratio and have become convinced that it is one of the most valuable electrocardiographic signs. This paper presents our conclusions regarding it.

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METHOD

Several hundred electrocardiograms, the majority of which showed a T_1 lower than T_3, were taken at random from our files. After elimination of incomplete and complete bundle-branch blocks, inverted T-waves in Lead I, most of the inverted T-waves in Lead III and all cases in which the diagnosis of heart disease was reported as doubtful, we had remaining 587 electrocardiograms. Inverted T_3 did not come within the scope of this study. For each electrocardiogram, the average QRS axis and the ratio of the height of T_1 divided by height of T_3 were determined. Other abnormalities, if present, were noted. A record was also kept of the presence or absence, and the relative amplitudes of the S-waves in all leads, and of the R-wave in Leads I and II.

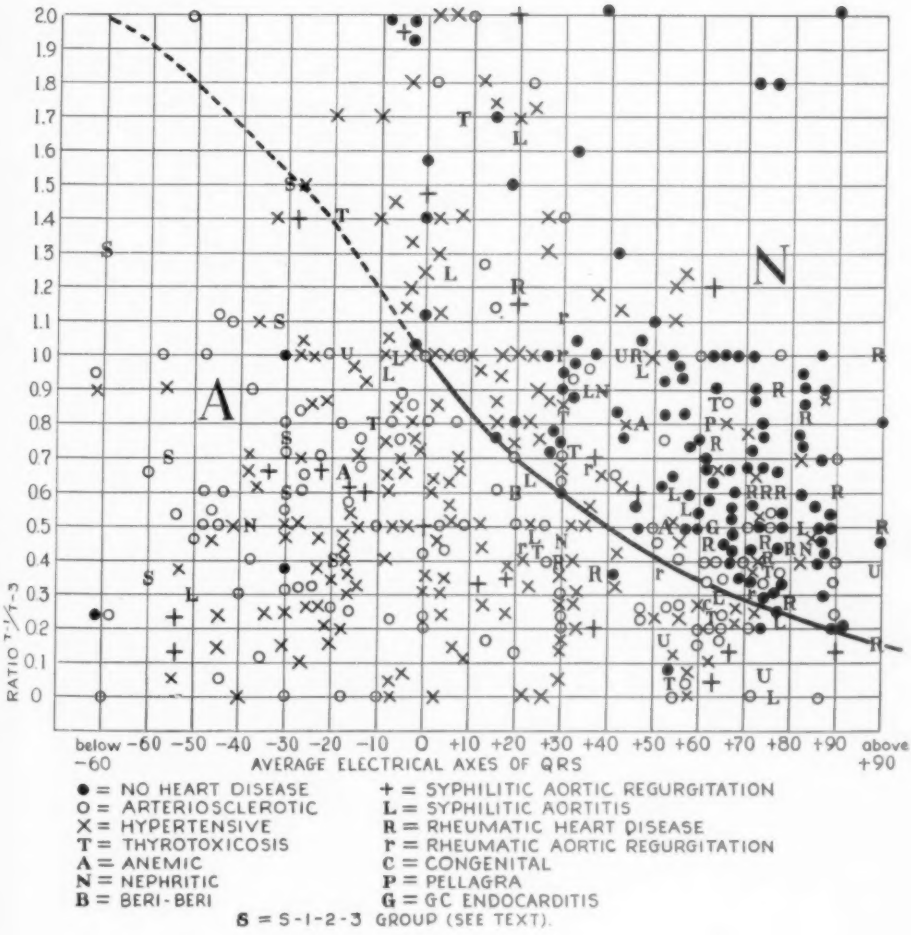

FIG. 1.

The T_1/T_3 ratio might have been expressed as the electrical axis of the T-wave, and the latter may readily be derived from the former. We felt the ratio to be more convenient.

Results

The average electrical axes of the QRS complexes and the T_1/T_3 ratios were plotted as shown in figure 1. The primary etiological factor is indicated by the sign used for each point, as explained on the figure. The points marked S constitute a special group which will be discussed below.

It will at once be seen that the great majority of the small black discs, corresponding to patients with no demonstrable heart disease, are located to the right of the oblique curved line. The placing of the line means, therefore, that according to our data, the ratio T_1/T_3 is normally smaller the more the average electrical axis of QRS inclines to the right, and vice versa. In damaged hearts, the normal ratio may be disturbed, as indicated by the points to the left of the line. We may say at once that we regard the area, N, above, and to the right of, the line as the normal, and the area A, below, and to the left of, the line as the abnormal area.

In table 1, only those points which fall between the ratios 0 to 2.00 are included in the subsequent analysis. Above 2.00 the ratio is normal for any QRS axis, except possibly extreme left axis deviations, while axes below 0, due either to T_1 or T_3 inversion, do not concern us. If we count the cases in each area, we find the following:

Table I

Etiology	Abnormal Area		Normal Area		Heart Station Population—500 cases Per Cent
	Number	Per Cent	Number	Per Cent	
No heart disease	6	2.5	101	42.4	22.6
Arteriosclerotic heart disease	77	32.0	33	13.8	17.0
Hypertensive-arteriosclerotic	115	48.0	59	24.8	35.0
Syphilitic aortic regurgitation	16	6.7	6	2.5	6.2
Syphilitic aortitis without regurgitation	8	3.3	7	2.9	4.6
Thyrotoxic	6	2.5	5	2.1	3.2
Rheumatic heart disease without aortic regurgitation	3	1.2	17	7.1	4.6
Rheumatic heart disease with aortic regurgitation	2	0.8	4	1.7	1.8
Congenital	1	0.4	0	0	1.0
Nephritic without hypertension	2	0.8	2	0.8	0.6
Anemic	1	0.4	0	0	1.8
Pellagra and beri-beri	1	0.4	1	0.4	0.4
GC endocarditis	0	0	1	0.4	0
Traumatic	0	0	0	0	0.4
Unknown	2	0.8	2	0.8	0.6
Totals	240	99.8	239	99.7	100

It will be seen from the table that 42.4 per cent of the 239 patients in the normal area were considered not to have heart disease, leaving 57.6 per cent who were diseased. In contrast, only 2.5 per cent (excluding the S group) in the abnormal area were considered to be without heart disease, leaving 97.5 per cent diseased.

The S group consists of eight patients, none of whom had demonstrable heart disease, and whose electrocardiograms are of a special and not very unusual type. There is either no trace, or the slightest trace only, of a Q-wave in any lead. R_2 is higher than R_1. A definite S-wave is present in all three leads, although S_1 is sometimes small. Both S_2 and S_3 are large. No upward deflection follows S in any lead. Among our 587 cases, 29, with QRS axes of + 20 or below, fell into this category. Only four of these 29 patients presented T_1/T_3 ratios lying within the normal area, but no doubt more would have done so had not our selection of electrocardiograms been mainly of the low T_1 type. Of these 29 cases, eight had no demonstrable heart disease; 19 had arteriosclerotic hypertensive heart disease; one, a male aged 44, was diagnosed beri-beri; while in another case the diagnosis of arteriosclerotic heart disease was regarded as doubtful. The percentage in this group without heart disease, 27.6, may be compared with the percentage of normals in the Heart Station population, or 22.6. Eleven of the 21 cases with definite or probable heart disease presented definite electrocardiographic abnormalities, while this was true of only one of the eight without demonstrable heart disease, and here the abnormalities (a P-R at the upper limit of the normal and a wide, but otherwise normal, P-wave) were borderline. None of the eight patients even approached the hypersthenic habitus. A transverse heart is not, therefore, usually responsible for this picture. On the contrary, it seems more characteristic of the vertical or normally placed heart. We have observed many other electrocardiograms of this type in patients without heart disease. We shall call such electrocardiograms the $S_{1\,2\,3}$ type.

Special attention should be directed to the six patients without definite heart disease and not of the special $S_{1\,2\,3}$ type, whose T-wave ratios fall in the abnormal area. On reëxamining the first case, at 75° and ratio 0.20, we find that because of irregularity of the base line, the amplitude of T_1 was doubtful. Reconsideration shows that it is unquestionably higher than as measured. This case actually, therefore, comes in the normal area and can be disposed of. We let it stand because of the obvious dangers to objectivity involved in reconsideration of difficult cases. The second case, at 55° and 0.07, is a colored male, 43 years of age. Although classified as normal, syphilitic aortitis was regarded as possible. The third case, at 44° and 0.35, was a colored male, aged 58. The peripheral arteries were sclerosed, but his heart was not enlarged and there were no cardiac symptoms. The fourth case, at — 30° and 0.38, was a white male, aged 50. His Wassermann was 4 plus and a diagnosis of tabes dorsalis had been made.

He complained of sharp pains "in his heart" on exertion or excitement. The fifth, at — 30° and 0.75, was a colored male, aged 28. He complained of rather severe, smothering, substernal pains on working, but nothing was found on physical examination. The Wassermann was negative. The sixth case, at 65° and 0.25 was a white male, aged 23. There was a marked deformity of the sternum which was sunken, forming a deep sulcus (funnel chest). He had experienced a right-side hemiplegia four months previously. A review of these six cases, therefore, indicates that in most of these instances the diagnosis of no heart disease was questionable.

Returning to the table, it will be seen that the various etiologic factors are not equally effective in producing abnormal T_1/T_3 ratios. Arteriosclerotic heart disease, without hypertension, constitutes 32.0 per cent of the abnormal and only 13.8 per cent of the normal ratios. The added presence of hypertension does not increase the tendency of the T-wave axis to deviate to the right. It should be noted that no attempt was made to separate the "essential" hypertensions or hyperpiesias from the hypertensive cases in which a nephritic factor was present.

If we may draw any conclusion from the small number of cases, syphilitic heart disease with damage of the aortic valve is just as potent, or even more potent, a factor than arteriosclerotic heart disease; while syphilitic aortitis, without valvular involvement may sometimes effect a rightward deviation of the axis. Thyrotoxicosis also appears to be effective, but this may depend upon factors other than the increased basal metabolic rate.

In contrast to the hypertensive-arteriosclerotic etiology is rheumatic heart disease when the aortic valve is not involved. The numbers indicate that this factor has little or no tendency to deviate the T-axis to the right. As a check against these figures, we have examined the electrocardiograms of the 100 children with rheumatic heart disease reported elsewhere by Drawe, Hafkesbring and Ashman.[5] Of these, 8 per cent showed abnormal ratios. Rather unexpectedly, the group with aortic valve disease showed no greater incidence of the abnormality than the others. These observations suggest that while rheumatic heart disease may sometimes cause an abnormal rightward deviation of the T-wave axis, such deviation is relatively infrequent. On the other hand, there is also no greater tendency for the T-axis to shift to the left.

It might be supposed that if there is enough myocardial damage to produce an abnormal T_1/T_3 wave ratio, the electrocardiogram would nearly always be otherwise abnormal. To afford information on this point, we give the data for the 68 electrocardiograms in the abnormal T-wave ratio area whose QRS axes are above + 20°. Of these, 11 cases, or 16 per cent, showed such extreme abnormalities of other kinds that the abnormal T-ratio was hardly needed as additional confirmation of the findings. There were 23 cases, or 35 per cent, in which the other abnormalities were moderate. In this group the evidence from the T-ratio was distinctly helpful. Finally,

33 cases, or nearly 49 per cent, showed no other abnormalities or such slight ones that their interpretation as abnormal depended entirely or almost entirely upon the abnormal T-wave ratio. In this latter group, of course, would fall many electrocardiograms whose QRS axes were below + 21°, but these are not here included because in them the left axis deviation itself might be regarded as abnormal.

It may be of some interest to observe, in figure 1, how the individual points just above, and to the right of, the oblique line and to the right of + 30°, are predominantly from patients with heart disease of the hypertensive-arteriosclerotic type. As the points lie deeper and deeper in the normal area, the proportion of such cases declines and that of no heart disease rises. This indicates that in many persons with heart disease the T-axis has begun to shift, but has not yet gone over into frankly abnormal territory. Perhaps a consideration of the anatomical axis of many of these hearts would indicate that their T-wave axes are, in fact, abnormal.

Discussion

The result of these comparisons suggests very strongly that rightward deviation of the T-axis is a result of disease of the left ventricle. Usually, but perhaps not always, the disease appears to be due to a relative or absolute inadequacy of the coronary circulation. Such inadequacy is obvious enough in arteriosclerotic-hypertensive heart disease. In aortic regurgitation the coronary flow is relatively inadequate; it fails satisfactorily to meet the increased oxygen demand resulting from the augmented ventricular diastolic volume. When syphilitic aortitis gives rise to symptoms, the orifices of the coronary arteries are likely to be involved by the pathological changes. Thyrotoxicosis, by increasing the oxygen demand, as well as the work, of the heart may often give rise to a relative coronary insufficiency. The left ventricle presumably suffers more than the right in these conditions, as is generally recognized, and as is indicated by the higher incidence of pathological changes in the left ventricle.

Myocardial depression or disease resulting from diphtheria does not cause a rightward deviation of the T-axis. On the contrary, the tendency is for it to shift to the left (Ashman and Hull [4]).

Large S_2. Proger and Minnich [2] have emphasized the importance as a sign of myocardial disease of a large S-wave in Lead II in left axis deviation. We are very much inclined to doubt the value of the large S_2 as an independent sign, for, in general, the larger the S_2 the greater the left axis deviation. It is the latter finding, and not the S_2, which is significant. Our data were analyzed from this standpoint and the results may be summarized as follows:

TABLE II

Electrical Axis	Large S_3		Moderate S_3		Small S_3		Trace of or No S_3	
	No H.D.	H.D.	No H.D.	H.D.	No H.D.	H.D.	No H.D.	H.D.
−40 to −59°	1	24	0	1	0	0	0	0
−20 to −39°	4	35	1	20	0	7	0	0
0 to −19°	2	19	3	32	3	28	3	11
+ 1 to +20°	1	5	4	21	0	29	2	34
Totals	8	83	8	74	3	64	5	45

It will be seen that there is no significant increase in the proportion of cases with no heart disease as the S_3 wave becomes smaller. However, as the electrical axis rises from about + 20, the incidence of cases with no heart disease rises. This is indicated by the table below, which is a continuation of table 2, and which follows the same headings.

TABLE III

+21 to +40°	0	5	9	14	8	28	3	15
+41 to +60°	2	2	5	9	11	26	6	20
Totals	2	7	14	23	19	54	9	35

These figures serve to emphasize the importance of the average electrical axis of QRS as an index of myocardial disease. In making an evaluation, however, the position of the heart must be considered, and the special $S_{1\,2\,3}$ group already described must be eliminated.

Low T_1. Another question which we have incidentally investigated is the absolute magnitude of T_1. Except for vertically placed hearts, Eideiken and Wolferth [1] place the lower limit of the normal height of T_1 at 2 mm. Our experience is in rather sharp contrast with their findings. The 100 adult normals, reported by Ashman and Hull,[4] had an average amplitude of T_1 of 1.7 mm. On reëxamining our records, we find that 51 of these subjects (or 51 per cent.) had T-waves in Lead I ranging from 1.8 mm. to 0.2 mm. The next lowest T-wave in this normal series was, however, 0.7 mm. Five of the 51 subjects were described as of hypersthenic habitus and their T_1 amplitudes were, respectively, 1.7, 1.4, 1.8, 1.3, and 1.5 mm., the corresponding average QRS axes being 62, 71, 0, 58 and 57°. Among the hundred individuals, not one had an abnormal ratio. The individual whose T_1 measured 0.2 mm. belonged, very clearly, in the $S_{1\,2\,3}$ group. It is not easy to explain the discrepancy between our findings and those of Eideiken and Wolferth. It may be that the T-wave tends to be lower in warm climates, a difference possibly associated with a lower basal metabolism (Hafkesbring and Borgstrom [6]). In this connection, it may be pointed out

that the average amplitude of T_1 as found by Lewis and Gilder [7] was 1.93 mm. The average amplitudes found by us were consistently about 0.2 mm. lower than theirs in each lead. But this small difference is quite insufficient to explain the discrepancy. The inclusion of a large number of young adult males in Eideiken and Wolferth's series may have some bearing on the difficulty, for the T-wave of males, both in children and in adults, is higher than that of females (Lincoln and Nicolson,[8] Pardee [9]). In a recent unpublished comparison, for example, we find the average height of the highest T-wave of the three leads to be about 2.65 mm. in adult males, against about 2.10 mm. in adult females.

Summary

In heart disease, and probably particularly when the left ventricle is more involved than the right, a rightward deviation of the electrical axis of the T-wave is a common finding. The deviation is most frequent in arteriosclerotic-hypertensive and in syphilitic heart disease; it is common in thyrotoxicosis; it is sometimes, but not often, seen in rheumatic heart disease.

The decision as to whether or not a given T-wave axis is abnormal depends upon the average electrical axis of the QRS complex.

A diagram is given which tentatively separates the normal from the abnormal T-wave axes at different QRS axes.

A special ($S_{1\,2\,3}$) type of electrocardiogram is described which is easily recognizable and which constitutes an exception to the general rule.

The significance of deep S_2 and of low T_1, as isolated findings, is discussed.

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CASE REPORTS

HYPERTENSION AND CONSTRICTION OF THE RENAL ARTERIES IN MAN: REPORT OF A CASE*

By Ebner Blatt and Irvine H. Page, *Indianapolis, Indiana*

We have recently studied a patient in whom the kidneys, adrenal glands, abdominal aorta, inferior vena cava, ureters, and renal vessels were enveloped in a firm mass of lymphosarcoma. This patient had arterial hypertension, and, since the renal vessels were markedly compressed by the tumor, it is suggested that this hypertension simulated that produced in dogs by constricting the renal arteries (Goldblatt, Lynch, Hanzal and Summerville [1]).

Case Report

The patient was first studied at the Cincinnati General Hospital in February 1937. He had had edema of the face, neck, and chest for one week. Roentgen-ray examination showed a right pleural effusion which had displaced the mediastinum to the left. Widening of the superior mediastinum and moderate infiltration of the right lung were observed several weeks later and were attributed to a lymphoblastoma. Partial superior vena cava obstruction was indicated by increased venous pressure in the arms.

He received roentgen-ray therapy from March until August 1937, when he was readmitted to the hospital with edema of the ankles. Venous pressure determinations now indicated partial obstruction of the inferior vena cava.

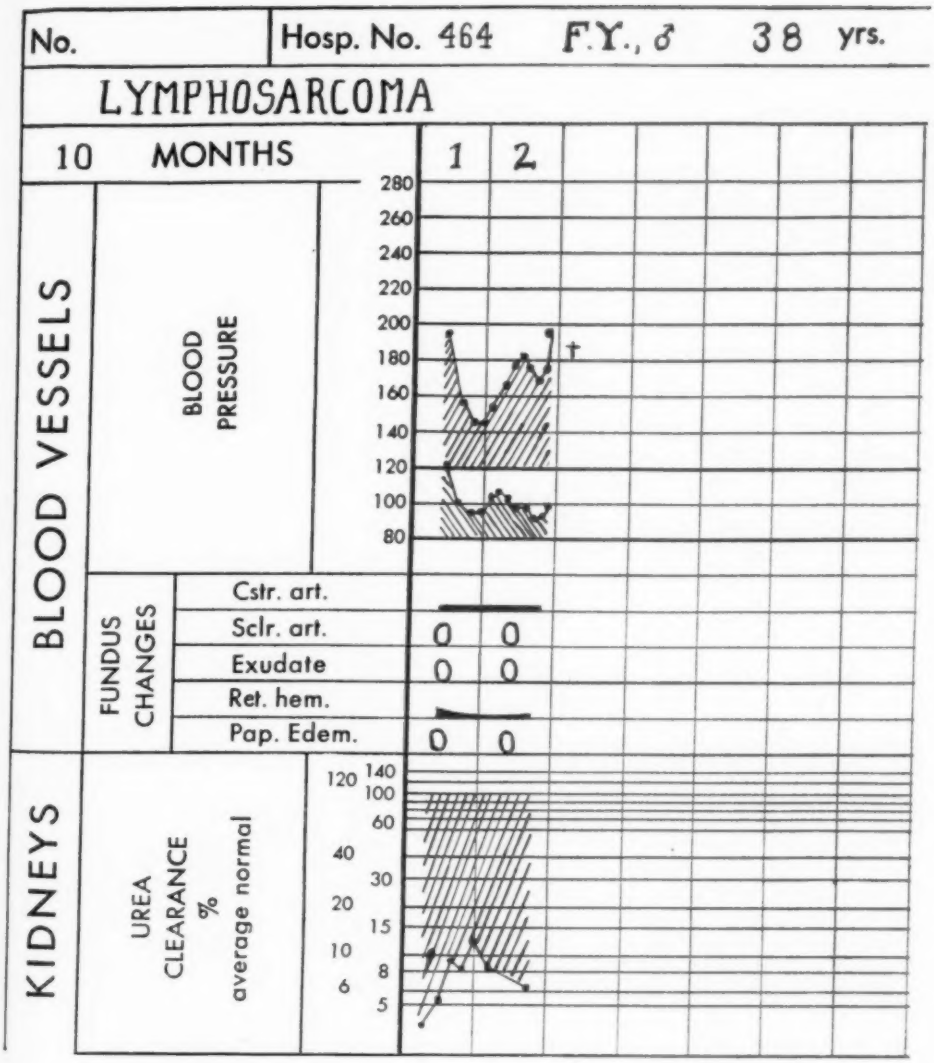
A week after admission he became drowsy and began to vomit. The blood urea nitrogen was 125 mg. per cent and the CO_2 combining power 26 volumes per cent. He was given large amounts of fluid intravenously and improved rapidly. All signs of uremia disappeared within three weeks. Repeated urine examinations showed no red blood cells and only a trace of protein. During his admission to the hospital arterial pressure varied from 150 mm. Hg systolic, 110 diastolic, to 135 systolic, 105 diastolic. The possibility that the uremia had been due to constriction of the renal arteries by a retroperitoneal tumor was suggested by the members of the staff of the Cincinnati General Hospital at this time.

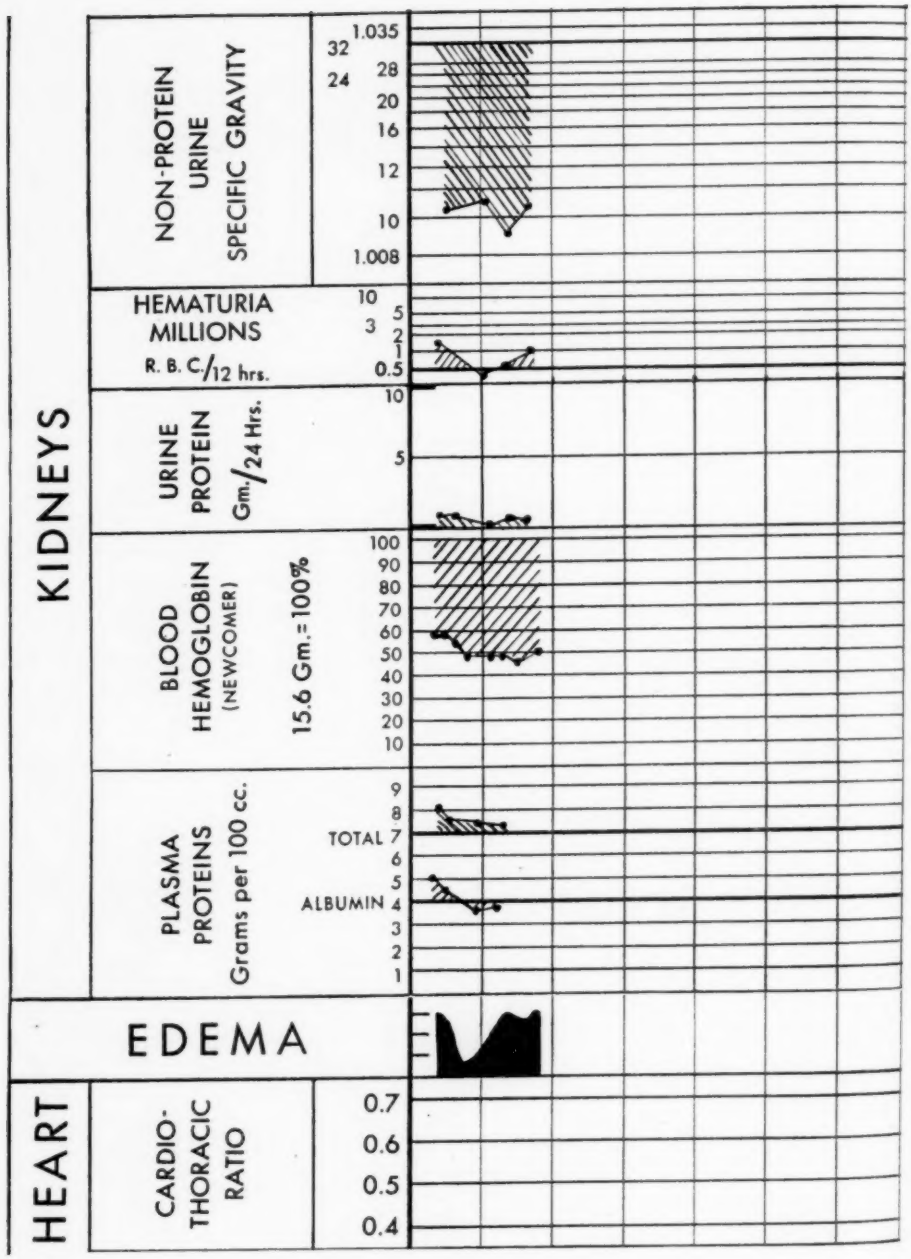
In October 1937, he began to have nocturia, and edema of the lower extremities recurred. He had had severe vomiting for several weeks before he was first seen at the Indianapolis City Hospital on November 9, 1937.

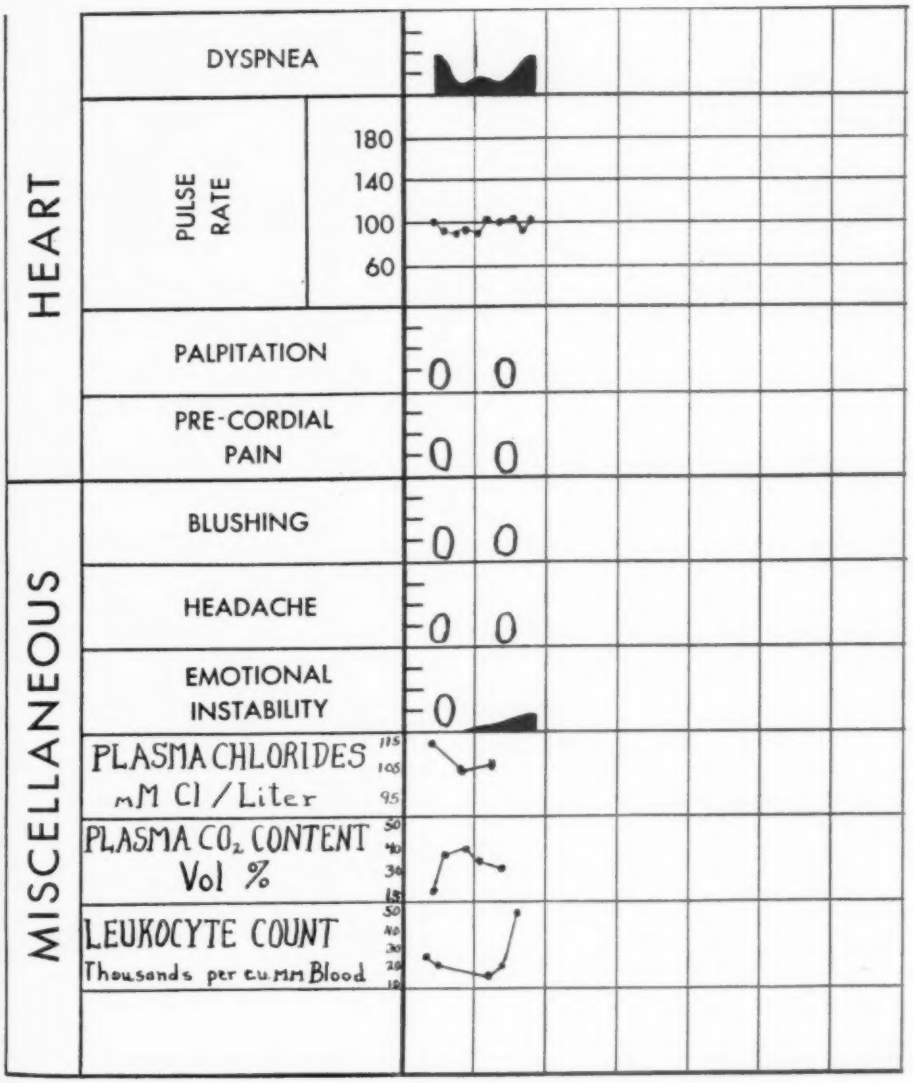
Physical examination now revealed marked pitting edema of the legs from the hips down. The scrotum was markedly edematous. There was slight edema of the eyelids and face. The heart was normal. There was fluid in the base of the right chest. The retinae showed a few small fresh hemorrhages and slight constriction of the arterioles. The blood pressure was 204 mm. Hg systolic, 110 mm. diastolic. The blood non-protein nitrogen was 250 mg. per cent and urea clearance 2.9 per cent of normal. (The results of the laboratory examinations are summarized on the accompanying graph.) Roentgenograms of the chest showed no evidence of a tumor.

* Received for publication March 26, 1938.

From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis, Indiana.


No.
Hosp. No. 464 F.Y., ♂ 38 yrs.
LYMPHOSARCOMA
10 MONTHS
1
2
BLOOD VESSELS
BLOOD PRESSURE
280
260
240
220
200
180
160
140
120
100
80
†
FUNDUS CHANGES
Cstr. art.
Sclr. art.
0 0
Exudate
0 0
Ret. hem.
Pap. Edem.
0 0
KIDNEYS
UREA CLEARANCE % average normal
120 140
100
60
40
30
20
15
10
8
6
5


KIDNEYS
NON-PROTEIN URINE SPECIFIC GRAVITY
1.035
32
24
28
20
16
12
10
1.008
HEMATURIA MILLIONS
R. B. C./12 hrs.
10
5
3
2
1
0.5
URINE PROTEIN Gm./24 Hrs.
10
5
BLOOD HEMOGLOBIN (NEWCOMER)
15.6 Gm. = 100%
100
90
80
70
60
50
40
30
20
10
PLASMA PROTEINS
Grams per 100 cc.
TOTAL
ALBUMIN
9
8
7
6
5
4
3
2
1
EDEMA
HEART
CARDIO-THORACIC RATIO
0.7
0.6
0.5
0.4


HEART
MISCELLANEOUS
DYSPNEA
PULSE RATE
180
140
100
60
PALPITATION
0 0
PRE-CORDIAL PAIN
0 0
BLUSHING
0 0
HEADACHE
0 0
EMOTIONAL INSTABILITY
0
PLASMA CHLORIDES
mM Cl / Liter
115
105
95
PLASMA CO_2 CONTENT
Vol %
50
40
30
20
LEUKOCYTE COUNT
Thousands per cu mm Blood
50
40
30
20
10

For about a week after admission edema continued to increase, and the patient's condition rapidly became critical. Since he had what appeared to be a lead line on the upper gum and increased numbers of reticulocytes and stippled red cells in his blood, he was given calcium carbonate and potassium bicarbonate by mouth, and calcium levulinate intravenously.

The patient seemed to improve for a week. Edema decreased and he lost 25 pounds of weight. Blood pressure dropped to 152 mm. Hg systolic, 102 diastolic and urea clearance rose to 9.5 per cent of normal. The venous pressure in his arms which had been 200 mm. of water was now 88 mm.

Edema of the lower extremities reappeared and increased steadily until his death. Arterial pressure rose to its previous high levels and urea clearance decreased. He began to show marked emotional instability. Two days before death he developed pain in the right side of the chest, dyspnea, fever, and tachycardia. Death occurred about 11 months after the onset of the disease.

Autopsy (Dr. H. C. Thornton and Dr. J. McFadden). There was a large firm neoplastic mass over the posterior abdominal wall. It enveloped the aorta, inferior vena cava, kidney, renal vessels, adrenal glands and ureters, and extended down into the pelvis and around the bladder. The mass and the structures involved in it were removed in a single piece weighing 1245 grams.

The aortic orifices of the renal arteries appeared normal in size, but cross sections through the mass showed that the arteries were constricted throughout their course. There was some hydronephrosis in both kidneys. The ureters were constricted throughout all but the terminal portions of their course.

Sections of the neoplasm proved it to be a lymphosarcoma composed of lymphoid cells and a reticular network of fine and coarse strands of connective tissue. Irregular infiltration of the lymphoid cells was present in both kidneys and was most marked around the hila. The outer epithelial layer of Bowman's capsule in many glomeruli was hypertrophied. The capillary lumina were narrowed and were empty of blood. The tubules were somewhat atrophic and their epithelium flattened. The kidney pelves were normal. The arteries within the kidneys were normal but the walls of the veins were infiltrated with lymphocytes. The ureters were normal except for constriction.

The adrenals were completely imbedded in the neoplasm but on microscopic examination the cells appeared normal.

The right lung was partially collapsed by cloudy fluid. The pleural surfaces of both lungs were grayish white with exudate. There was no consolidation in either lung.

The pituitary gland, liver, heart, spleen, pancreas, bladder, prostate, stomach, intestines and brain were normal both on gross and microscopic examination.

The bone marrow was normal on inspection but microscopic study showed it to be very cellular with preponderance of lymphoblastic cells.

Discussion

Since the lymphosarcoma involved the kidneys, renal vessels, ureters, abdominal aorta, inferior vena cava and adrenal glands, and since the kidneys showed histologic evidence of early glomerulonephritis, the possible factors entering into the genesis of arterial hypertension in this patient are numerous.

The hemorrhages in the retinae, constriction of the retinal arterioles, proteinuria and hematuria, although all of minor degree, suggest the occurrence either of chronic glomerulonephritis or of essential hypertension. However, from pathological examination, the evidence of glomerulonephritis was slight.

FIG. 1. Posterior view of lymphosarcoma and structures enveloped in it. The aorta is partially opened. The white lines indicate planes through the mass which are shown in figure 2.

It consisted of hypertrophy of the outer layer of Bowman's capsule, hyalinization in a few glomeruli, and atrophy of some of the tubules. The absence of cardiac hypertrophy and of widespread degenerative changes in the arteries, and the relatively short duration of the disease mitigate the probability of essential hypertension.

Among the methods designed to produce hypertension of renal origin are: reduction of the amount of functioning renal tissue; permanent or temporary occlusion of the renal arteries, veins, and ureters; passive hyperemia by constriction of the renal vein; permanent or temporary obstruction of the ureters; and compression of the kidneys by an oncometer. With most of these methods

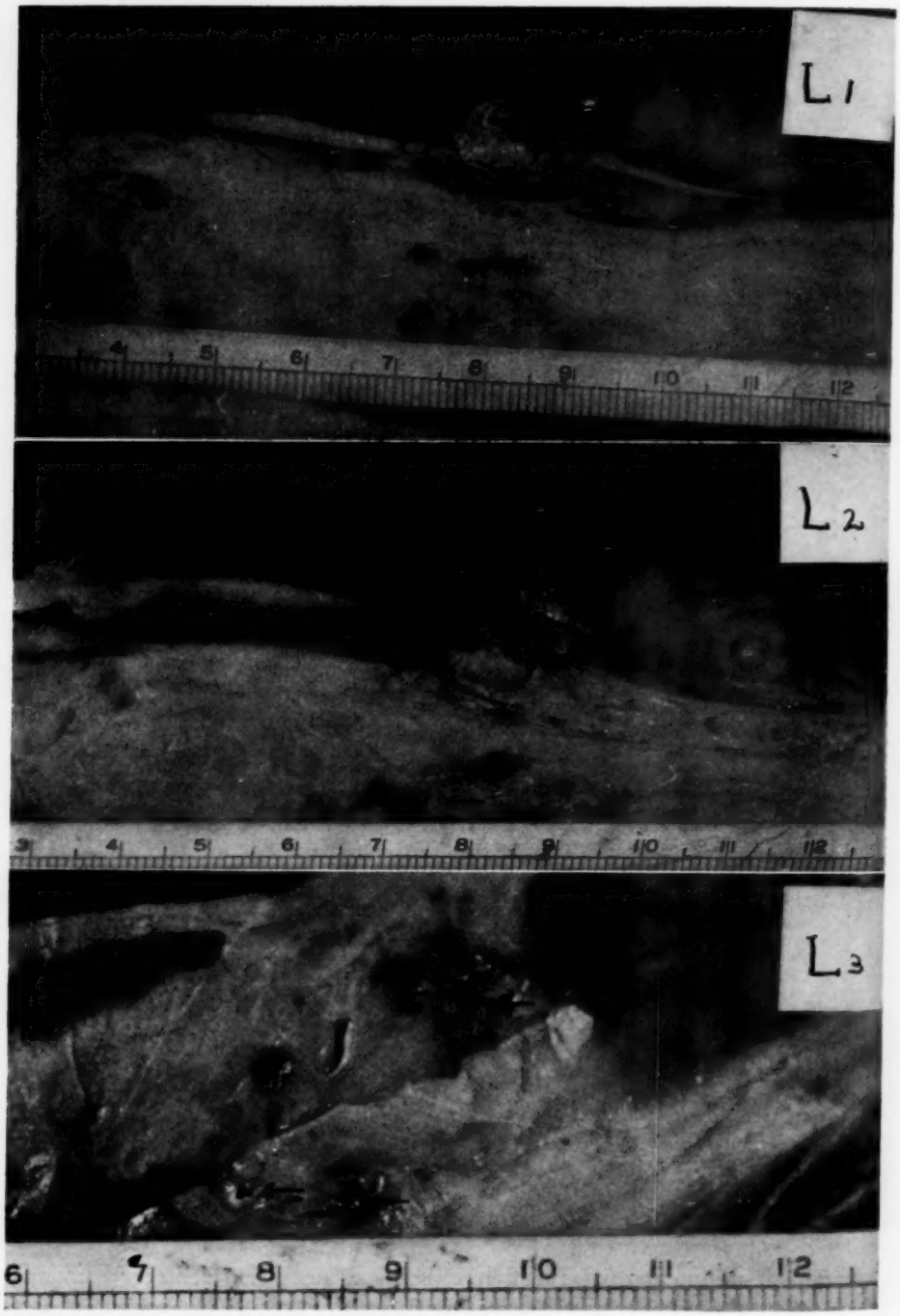
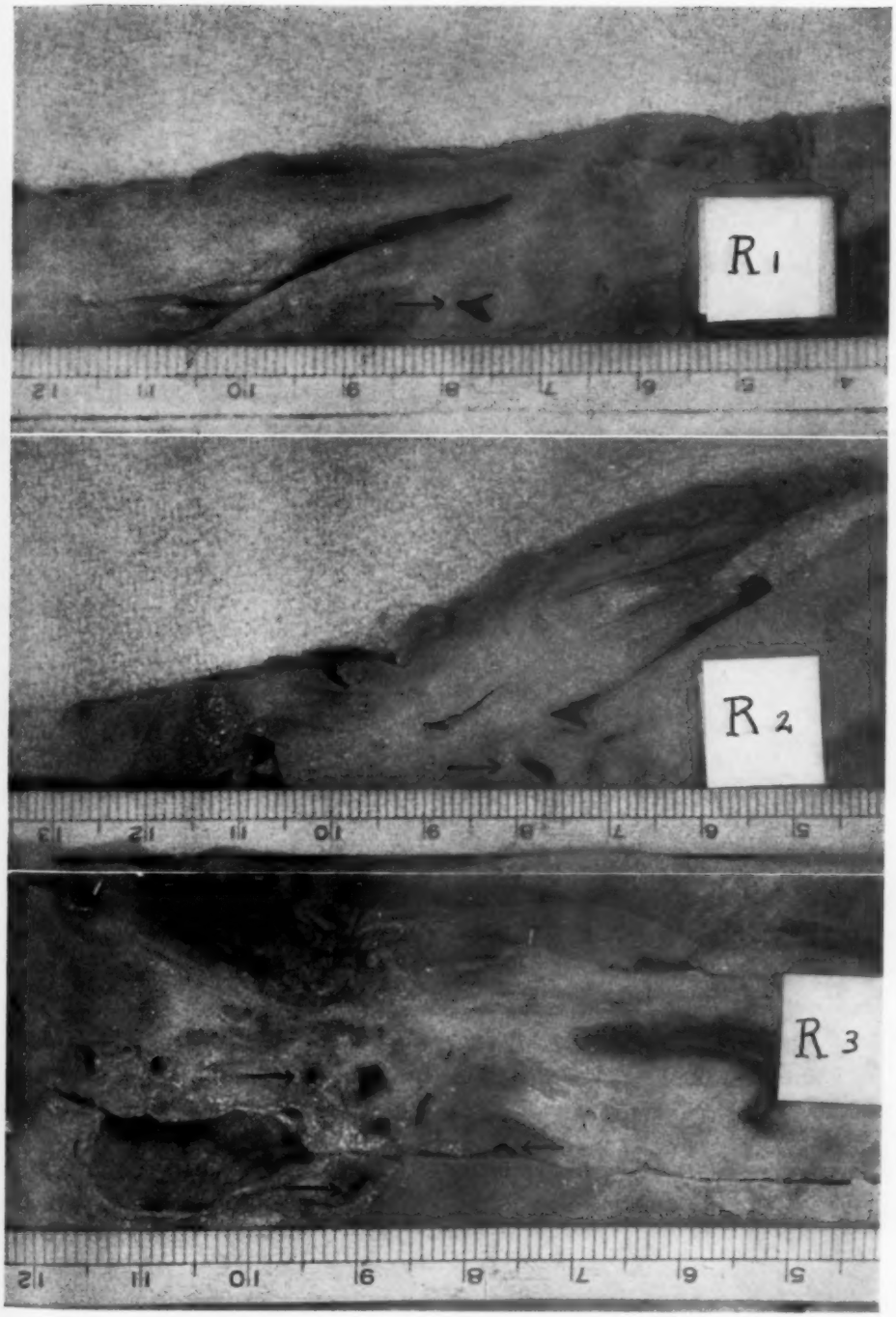


FIG. 2. Cross sections through the neoplastic mass showing compression of the renal arteries. The arrows in each picture point to the renal artery or its branches. The



identification number on each picture indicates the plane through the neoplasm as shown in figure 1.

FIG. 3. Section of kidney cortex showing hypertrophy of outer layer of Bowman's capsule in two glomeruli, atrophy of tubular epithelium, and infiltration of kidney substance with lymphoid cells. The lumina of the glomerular capillaries are devoid of blood.

the hypertension is only moderate in degree and is usually transient.[2] This contrasts with the severity of the hypertension produced by partial constriction of the renal arteries. The accompanying photographs clearly demonstrate that the renal arteries of the patient were definitely constricted.

It is interesting to note that the severity of the hypertension and the reduction of urea clearance closely paralleled the amount of edema in the lower extremities. This seems significant if it is an indication that the degree of constriction of the renal arteries varied with the degree of constriction of the aorta and vena cava. However, in dogs the degree of hypertension does not always increase with increased constriction of the renal arteries. Furthermore, hypertension can be produced by constriction of the renal arteries too slight to alter the renal clearances.[3]

Conclusion

A patient with arterial hypertension was studied in whom the genesis of the hypertension was apparently due to partial constriction of the renal arteries simulating the production of experimental hypertension by the Goldblatt clamp.

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HEMOLYTIC REACTION FOLLOWING BLOOD TRANSFUSION; REPORT OF A CASE OF INTRA-GROUP INCOMPATIBILITY *

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Before the days of blood grouping, hemoglobinuria was a common sequel of blood transfusion, and in many of the cases renal insufficiency developed, usually with lethal termination. Such hemolytic transfusion reactions were first described by Denys [1] in 1667. Their frequent occurrence in his cases was not surprising, for he had been injecting sheep's blood into human beings. However, similar reactions occurred in a large percentage of the cases where human blood, exclusively, was transfused. This served as a barrier to the wide usage of blood transfusion as a therapeutic measure.

In 1900 and 1901, Landsteiner [2] showed that the serum of certain normal individuals can agglutinate or hemolyze the red blood cells of certain other normal individuals. On the basis of his studies, he was able to identify three

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distinct groups. The fourth blood group (AB) was described in 1902 by Decastello and Sturli,[3] the latter a pupil of Landsteiner.

When donors are selected according to their blood groups, blood transfusion is a relatively safe procedure. Where hemolytic reactions have occurred, in the vast majority of the cases errors in blood grouping have been responsible, as shown by Bordley.[4] The second most common cause of hemolytic reactions is the indiscriminate use of the so-called universal donor for recipients not belonging to group 0. In a minority of the cases, hemolytic reactions have been traced to the presence of atypical agglutinins in the recipient's serum, which agglutinated the donor's red blood cells.[5, 6] Such cases can be detected by cross-matching.

Therefore cross-matching has been added to blood grouping as the routine procedure in determining compatibility before transfusion. Despite these precautions, however, reports of hemolytic reactions, where careful blood grouping and cross-typing had been observed, continue to appear.[7, 8] Fortunately such cases are rare. The unusual clinical features of such a case, recently seen, warrant a detailed report.

Case Report

L. E. D., 38 years of age, was admitted in labor to the Jewish Hospital of Brooklyn * May 24, 1937, and discharged July 24, 1937.

Family history. Her father had been treated for malignant hypertension for years, and died following a hemiplegia. Her mother was an advanced arteriosclerotic with hypertension.

Past personal history. There had been no illness, excepting influenza in 1918. There had been three pregnancies (1924, 1925 and 1935), each terminating prematurely in the seventh month. Hypertension complicated the last pregnancy (1935); the blood pressure reached 160 systolic and 106 diastolic; the urine was normal; the blood Wassermann test, normal; and blood chemical tests were reported as follows: Urea, 11.06 mg. per 100 c.c.; uric acid, 4.1 mg. per 100 c.c.; CO_2 combining power, 42.9 volumes per cent. A few days after delivery, her blood pressure returned to normal.

In November, 1936, she became pregnant. Her blood pressure was 180 systolic, 100 diastolic. During the succeeding months it ranged between 142/80 and 190/100. Frequent urine analyses revealed no abnormal findings. On April 13, 1937, because of increasing headaches and persistent hypertension, she was admitted to the hospital for further study. The physical examination disclosed nothing remarkable; the eye grounds were normal. Laboratory studies revealed the following data: There was no negative water balance; the kidneys diluted well and concentrated well (1.002 to 1.028). Phenolsulphonephthalein test showed that a total of 86.6 per cent of the dye was excreted in two hours, 68 per cent in the first hour. Non-protein nitrogen, 17.7 mg. per 100 c.c.; urea, 9.9 mg. per 100 c.c.; uric acid, 3.1 mg. per 100 c.c.; creatinine, 1.7 mg. per 100 c.c. The urea clearance was 112 per cent of normal the first hour, and 101 per cent of normal the second hour. The blood pressure was 198/112 on admission, rose to 210/130 the day following, then gradually declined, reaching 150/110 on the sixth day. Because of prematurity of each of her preceding pregnancies, it was decided not to interrupt this pregnancy.

Present admission. The patient went into labor at 4 p.m., May 24, 1937. Her blood pressure was 276/160. A male child was delivered at 11:15 p.m.

May 25: Blood continued to ooze from the vagina, her pulse rate rising steadily. At 4 a.m. she complained of weakness, the skin was cold and clammy, her pulse rapid

* On the private service of Dr. S. G. Blum.

and of poor volume. She was returned to the operating room, and the uterus was explored; some decidua and blood clots were removed, and a tear in the cervix sutured. The patient was returned to her room in shock and a transfusion was ordered.

The patient's blood was grouped with standard sera of high potency and found to belong to group A; her husband's blood was also found to belong to group A; cross-matching was performed and the blood samples found to be compatible. A transfusion of 500 c.c. of blood was given by Dr. A. S. Wiener, by the direct method. No immediate reaction was observed during the transfusion. No chills or fever were noted after the transfusion. A continuous intravenous infusion of physiologic saline was given during the rest of the day. Her general condition remained unchanged.

May 26: The patient appeared somewhat better. She had not voided since delivery. At 4 p.m. (30 hours after the transfusion) three ounces of a turbid, dark red urine were obtained by catheterization. The blood pressure was 160/110.

May 27: The patient was very restless, the pulse was rapid and of small volume; pruritus was marked; small petechiae were found widely scattered over the body; the sclerae showed a slight icteric tint. At 4 a.m., catheterization yielded one half ounce of a turbid, dark red urine; at 4 p.m., none was obtained after catheterization. The blood pressure was 130/95.

May 28: The patient was drowsy, slight nuchal rigidity was evident, and coarse muscular twitchings were observed in all the extremities. The heart sounds were of better tone, the pulse rate was 96 and of better volume. Her blood pressure was 125/105. The liver was felt an inch below the costal border. There was tenderness in the right flank. The eye grounds were normal. Catheterization at 4 a.m. and at 4 p.m. yielded an ounce of turbid, dark red urine.

May 29: The patient was incoherent, pruritus was marked; icterus was evident in the skin and sclerae; the pupils were pin-point in size; the neck showed slight rigidity. Slight edema was evident over the face and extremities. The liver edge was felt three inches below the costal border. The right kidney was markedly enlarged and tender. Large purpuric areas appeared over the trunk and extremities. The patient voided four ounces of a turbid, dark red urine. The blood pressure was 235/140.

May 30: The patient was coherent. Rigidity of the neck was no longer demonstrable and the coarse muscle twitchings were only occasionally evident. The skin appeared more edematous; new crops of purpura were seen. The pruritus was intolerable. A soft, blowing systolic murmur was heard over the mitral area. The patient voided six ounces of a turbid, dark red urine. The icteric index was 23. Her blood pressure was 160/100.

May 31: At 3 p.m., the patient was seized with a paroxysm of coughing that lasted 15 minutes, followed by expectoration of blood-streaked sputum. The heart rate was accentuated, the sounds were of good quality; the mitral systolic appeared somewhat harsher than the day previously. The lungs showed nothing remarkable. Seven ounces of a turbid, brown-red urine were passed. The blood pressure was 195/130.

June 1: The skin appeared darker (bronzed) and more edematous; fresh crops of purpura appeared. The liver edge was felt two inches below the costal edge and was less tender. Ten ounces of a dark brown urine were passed. The blood pressure was 170/110.

June 2: Several areas of induration appeared over the lower back which caused the patient considerable pain. The pruritus continued a source of great discomfort. Nine ounces of dark amber urine were voided. The blood pressure was 160/105.

June 3: The skin was more edematous, the bronzing more distinct. A peri-

cardial friction rub was evident over the entire precordium. The lungs were clear. The liver was felt at the costal edge. The patient voided 10 ounces of turbid, dark amber urine. The blood pressure was 155/95.

June 4: The patient complained of severe precordial pain. Dyspnea was marked. The pericardial friction murmur persisted. Dullness and diminished breathing were noted over the left base and axilla. Nine ounces of urine were passed. The blood pressure was 155/95.

June 5: The edema of the skin was so marked that patient complained of "tightness of the skin"; it was decidedly bronzed, and the pruritus had not abated. The areas of induration over the lower back had formed into four large carbuncles. The pericardial friction sounds could be heard all over the precordium. An effusion had developed in the left chest, reaching to the angle of the scapula. Frequency of micturition was evident, and 30 ounces of urine were passed. The blood pressure was 150/95.

June 6 and June 7: There were no changes noted. The urinary excretion balanced the total fluid intake (1500 c.c.) The blood pressure was 130/85.

June 8: The skin appeared less edematous; the bronzing and the pruritus continued, unchanged. The pericardial friction murmur could be heard only toward the base of the heart. The pleural effusion had appreciably diminished. The carbuncles appeared larger. The total fluid intake was 1500 c.c.; the output, 1200 c.c. The blood pressure was 150/95.

June 9: The pericardial friction murmur was no longer evident and the effusion apparently had been completely absorbed. Diuresis was marked, the patient voiding 2400 c.c. of urine. The blood pressure was 160/112.

June 10: The edema was no longer evident. The bronzing of the skin was not as deep, but the pruritus continued, unabated. The intake was 1200 c.c., the output 2700 c.c.

June 11: The icteric index was 5. The total fluid intake was 2100 c.c., the output 2500 c.c. The blood pressure was 140/95.

June 12: The skin appeared lighter; the pruritus continued unrelentingly. The systolic murmur heard over the mitral was decidedly louder and roughened. Central areas of softening appeared in the carbuncles. The total fluid intake was 1800 c.c., the output, 2000 c.c.

June 13: The carbuncles had begun to drain, status otherwise unchanged. Intake, 1600 c.c.; output, 1200 c.c.

June 14 to June 23: The skin gradually lost its pigmentation; the pruritus, however, continued, uninfluenced by therapy; the mitral systolic murmur persisted, loud and harsh; the water metabolism was well balanced; the carbuncles drained freely; the blood pressure remained at a level of 130/80.

June 24: Another carbuncle had developed at the base of the spine. At 4 p.m., the patient developed an attack of dyspnea, her skin became cold and clammy, and the pulse rapid and feeble. After a half hour, all symptoms had disappeared. There were no changes in the cardiac or pulmonary findings.

June 25 to June 28: The carbuncles were draining freely. The lungs were clear, the systolic murmur in the mitral area was loud and harsh. The water metabolism continued balanced, the blood pressure remained at the former level, the pruritus seemed to be less troublesome.

June 29: At noon, the patient had an attack similar to the one on June 24. The dyspnea, however, continued all day, and there were several paroxysms of coughing, with expectoration of blood-streaked sputum. The heart rate became somewhat accelerated; toward evening a few crepitant râles were heard over the base of the left lung.

June 30: Showers of crepitant râles were heard over the left base. In the after-

noon broncho-vesicular breathing was noted over the left base. In the evening, effusion of the left chest was evident, reaching to the angle of the left scapula.

July 1: The patient was not dyspneic or cyanotic; she coughed frequently with expectoration of non-odorous, green muco-pus. Flatness was obtained all over the left chest, anteriorly, posteriorly and in the axilla; the breath sounds were not heard. The heart was not displaced; the murmur heard over the mitral area was softer; the pulse rate was 96.

July 2 to July 3: The cough and expectoration were less marked. Roentgenogram of the chest revealed considerable fluid in the left chest, the heart not displaced and the right lung field clear.

July 4: Diagnostic thoracentesis; 60 c.c. of a cloudy, straw-colored fluid removed. Culture was subsequently reported negative. The fluid was rich in proteins and coagulated spontaneously on standing.

July 5 to July 11: The patient was comfortable, the pruritus was definitely improved. The pleural effusion gradually was absorbed. The heart was regular, of good quality and the soft systolic murmur over the mitral area persisted.

July 12 to July 16: Another carbuncle developed over the left buttock. This was incised on July 16.

July 17 to July 24: The patient out of bed. The heart was of normal size, a soft systolic murmur was present over the mitral area. The lungs were clear. All the carbuncles were draining freely. The blood pressure was 130/90.

Subsequent course: The patient has remained in good health since discharge from the hospital. The carbuncles did not completely heal until late in September. The kidneys concentrate well, the blood pressure ranges between 130/90 and 150/95, the soft mitral systolic has persisted.

Summary of temperature record: There was no chill or temperature elevation following the transfusion. The temperature did not rise above 100° until two weeks later. Then, with the appearance of the cardiac murmur and the carbuncles, it became remittent, never exceeding 103°. It continued, thus, from June 7 to July 15. After July 15, the peak of the temperature declined daily, reaching normal five days later.

Summary of laboratory data.

Urine analyses. The first specimen of urine, after delivery, was the three ounces obtained by catheterization 30 hours after transfusion. This was turbid, dark red, and showed the presence of free hemoglobin chemically and spectroscopically; no red blood cells or leukocytes were found. Free hemoglobin was detected in all subsequent samples until June 3. Red blood cells were first noted May 29, increased in amount up to June 3, then progressively decreased numerically and finally disappeared June 8. Leukocytes were first found in the urine on May 30, increased in number and were also reported in clumps, up to June 6, then became less numerous in subsequent specimens. The reaction of the urine was always alkaline. The specific gravity varied from 1.006 to 1.018.

Blood and differential counts and hemoglobin determinations are presented in figure 1 and table 1.

Blood chemistry studies. The extent of the azotemia is graphically shown in figure 1. It will be noted that the blood chemistry findings were normal one month before delivery. Following transfusion, there was an abrupt azotemia. The urea increased to 60.3 mg. per cent on May 27, mounted steadily to reach a peak of 215.5 mg. per cent on June 8, then gradually declined reaching 44.4 mg. per cent on September 4. The non-protein nitrogen curve paralleled the urea curve, reaching 262.2 mg. per cent on June 8, then gradually declined. The creatinine reached its peak of 16 mg. per cent on June 3, then gradually fell, reaching 3 mg. per cent on Sept. 4. The uric acid reached 21.9 mg. per cent on June 5, then steadily declined. The CO_2

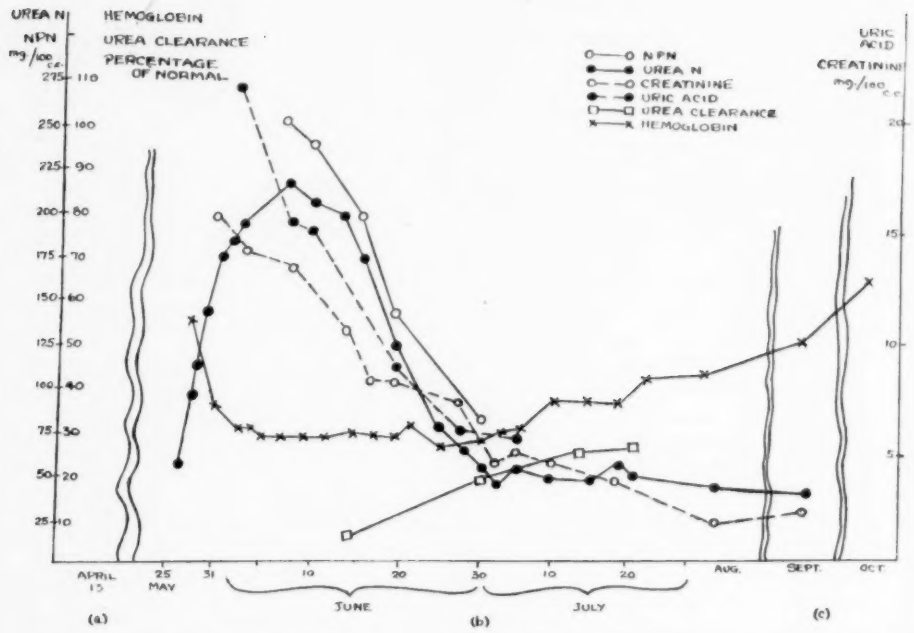

FIG. 1. The blood chemical studies: (a) during the period of the patient's stay in the hospital in April, all findings were normal; (b) during the period following the blood transfusion; and (c) after her discharge from the hospital.

TABLE I

Blood and Differential Counts, and Hemoglobin Determinations

Date	R.B.C.	Hgb.	W.B.C.	Polys.	Eosin.	Bas.	Lymph.	Monocytes	Reticulocyte
5–30	2,700,000	56%	32,900	84%	0%	0%	14%	2%	
6–1	2,200,000	37%	31,400	82%	0%	0%	18%	0%	
6–3	1,870,000	33%	33,000	92%	0%	0%	7%	1%	
6–4	1,780,000	33%							
6–5	1,330,000	30%	21,700	90%	0%	0%	9%	1%	
6–7	1,590,000	30%	25,950	96%	0%	0%	2%	2%	
6–9	1,510,000	30%	26,150	94%	0%	0%	6%	0%	
6–11	1,440,000	30%	29,350	95%	0%	0%	5%	0%	2.5%
6–14	1,850,000	31%	32,300	94%	0%	0%	6%	0%	5%
6–16	1,450,000	31%	29,900	97%	0%	0%	3%	0%	
6–18	1,640,000	31%	13,900	92%	0%	0%	8%	0%	1.6%
6–21	1,650,000	34%	11,500	90%	0%	1%	9%	0%	
6–25	1,330,000	29%	9,400	93%	0%	0%	7%	0%	
6–29	1,350,000	32%	11,750	80%	0%	0%	20%	0%	
7–2	1,990,000	34%	11,800	86%	0%	0%	14%	0%	
7–6	1,700,000	34%	9,300	84%	0%	0%	16%	0%	
7–10	2,500,000	40%	17,250	83%	1%	0%	16%	0%	
7–15	2,030,000	40%	9,100	74%	0%	0%	24%	2%	
7–19	2,580,000	40%	8,300	70%	2%	0%	24%	4%	
7–23	2,590,000	47%	9,550	76%	0%	0%	24%	0%	
8–2	3,210,000	49%	8,700	72%	0%	0%	25%	3%	
9–4	3,840,000	70%	7,600	74%	1%	1%	22%	2%	
10–2	4,240,000	76%	6,900	77%	1%	0%	22%	0%	

combining power was 34.2 volumes per cent on May 31, then ranged between 40.2 and 47.5 volumes per cent.

The urea clearance one month before delivery was 110 per cent of the average normal. On June 16 it was 7½ per cent, then slowly increased, reaching 25.5 per cent of normal on June 22.

The results of the determinations of blood proteins, as well as of the albumin and globulin fractions are shown in table 2.

TABLE II

Blood Protein Studies (in gm. per 100 c.c. of serum) During and Following the Period of Edema

Date	Total Protein	Alb.	Glob.	*A/G* Ratio
6–8	5.04	2.20	2.84	0.77
6–11	5.67	2.05	3.62	0.57
6–21	5.19	2.13	3.06	0.70
6–29	6.35	3.37	2.98	1.13

Blood cultures. No growth was reported on blood cultured on June 14, June 30 and July 2.

DISCUSSION

In general the mortality due to blood transfusion varies in different clinics from 0.2 per cent to 1 per cent depending on the technic used. A good proportion of these deaths can be traced to hemolytic reactions with renal insufficiency. In most cases, symptoms become manifest during or immediately following the transfusion, viz., pain in the lumbar region, a cold, clammy sweat, a sense of constriction in the chest, and varying degrees of shock; chills and fever usually follow. Partial or complete suppression of urine, with hemoglobinemia and hemoglobinuria are characteristically present; itching and jaundice may become apparent within 48 hours, and in most cases, edema develops. With the suppression of renal function, clinical uremia appears, with increasing azotemia; (in Baker and Dodds'[9] case, the urea rose to 920 mg. per 100 c.c. and the creatinine to 26 mg. per 100 c.c.).

In the cases [8, 9, 10] that came to autopsy, the description of the basic pathology was similar. There was dilatation of the tubules caused by the plugging of the tubular system with a substance in the form of small masses and granules of varying size, that stained with eosin. The tubules showed a varying degree of degeneration of their epithelium, not unlike the picture of mercurial nephrosis. The convoluted tubules and Henle's loops were most frequently involved. In several cases, focal hepatic necrosis has been described.

MECHANISM OF THE PRODUCTION OF SUPPRESSION OF RENAL FUNCTION

The obstructive theory has most advocates. DeGowin et al.,[10] by injecting solutions of hemoglobin into the blood of dogs, Yorke and Nauss [11] and Baker and Dodds [9] by similar experiments in rabbits, and Melnick et al.[12] by repeated infusions of red blood cells into dogs, reproduced the clinical and pathological picture of renal suppression due to obstruction of the tubules. They have shown that the kidney readily excretes hemoglobin as oxyhemoglobin when the reaction

of the urine is alkaline. When the reaction is acid, precipitation of the hemoglobin occurs with obstruction of the renal tubules. This precipitation was augmented in the presence of a concentration of sodium chloride above 1 per cent. Newman and Whipple [13] demonstrated the deposition of hemosiderin in the convoluted tubules of the kidney and in the liver, spleen and lymph nodes as well.

Spasm of the Renal Vessels. Mason and Mann [14] produced vasoconstriction of the renal arteries by intravenous injections of hemoglobin. Hesse and Filatov [15] obtained similar results and concluded that the spasm of the renal arteries accounted for the failure of renal function. They found that transfusion of compatible blood relaxed the spasm of the renal arteries and restored renal function.

When a hemolytic reaction has occurred, the possibility of an error in blood grouping must first be considered. Bordley [4] stressed the necessity of rechecking the blood grouping in such cases. In my case, when samples of blood from the patient and the donor, her husband, were examined before the transfusion, they were found to belong to group A and to be compatible on cross-matching. Three days after the transfusion, fresh blood specimens were taken from the donor and recipient and studied by Dr. A. S. Wiener.* He confirmed their group A classification and found them compatible on cross-matching. He further found that while the donor belonged to sub-group A_1, the recipient belonged to sub-group A_2. It was his opinion, however, that although they belonged to different sub-groups, this was not sufficient to account for the hemolytic reaction, since he was unable to demonstrate any agglutinins or hemolysins in the patient's serum which could act on the donor's red blood cells, or vice versa. Evidently this is another instance of an in vivo incompatibility which could not have been predicted by any of the present in vitro tests.

My patient showed all the characteristics of a transfusion hemolytic reaction: a protracted period of shock, complete and incomplete suppression of urine and clinical uremia with marked azotemia. Free hemoglobin was found in the serum and urine, jaundice developed, the icterus index was increased and pruritus was marked. The edema that developed was of the nephrotic type, the blood showing the characteristic reversal of the A/G ratio (table 2).

There were several distinctive features of this case that warrant further discussion. (1) The lack of the immediate symptoms that characterize these hemolytic reactions was probably masked by the protraction of the initial shock. No chills or temperature elevation were evident. (2) Pruritus developed 48 hours after the transfusion, and continued unabated for several weeks, resistant to all therapeutic measures. (3) When the azotemia reached its peak, pericarditis developed, occasioned considerable pain in the chest and lasted several days. (4) A systolic murmur was heard over the mitral area on the sixth day. At first soft, of short duration and of slight intensity, it later became rough, louder and filled all of systole. Finally, it returned to its original character. The murmur was still evident six months later. (5) The three embolic pulmonary episodes were probably secondary to a non-septic thrombo-phlebitis. However, the presence of an endocardial lesion, the irregular temperature and

* Dr. Wiener also tested the blood specimens for their properties, M and N, and found that both belonged to type MN.

the repeatedly negative blood cultures in the presence of embolism, suggest the possibility of a non-bacterial thrombotic type of endocarditis such as has been described by Gross and Friedberg [16]; the embolus, arising from its mitral seat, may have passed through one of the bronchial arteries to reach the lungs. (6) The purpuric eruption became widespread; the ecchymotic area over the lower back became the seat for the subsequent development of several carbuncles. The platelets at all times appeared adequately distributed over the blood smear. There was no bleeding from the mucous membranes such as occurs with the prothrombin or fibrinogen deficiency that characterizes anaphylactic reactions. The capillary endotheliotoxic action of some unknown retention product of uremia was probably the responsible cause. (7) The nephrotic picture resembled closely that of mercurial nephrosis. Erlanger [17] has shown that in the later stages of severe shock, the vessel walls become permeable to protein which, therefore, escapes from the blood into the extracellular spaces and transudates. (8) The distinct bronzing of the skin associated with hepatomegaly suggested widespread deposition of hemosiderin, as was experimentally shown by Newman and Whipple.[13]

Treatment. The protracted period of shock and the low hemoglobin and erythrocytic values raised the question of the advisability of giving another transfusion, using another donor (Hesse and Filatov [15]). However, when no assurance could be given the family that another reaction would not be summated on the other, further plans for such a procedure were abandoned. The anemia was treated by oral administrations of iron and parenteral liver extract.

The value of an alkaline urine had been established in the experimental animal. An alkaline urine favors the excretion of hemoglobin as oxyhemoglobin. Sodium bicarbonate in doses of 10 gr. four times daily was well tolerated by mouth and proved sufficient to keep the urine alkaline. The use of larger doses of alkalies may cause alkalosis in these patients, because of the lack of adjusting power of the kidneys (Peters,[18] Ellis [19]).

The great difficulty lies in reëstablishing renal function. The routine adapted by Peters et al.[20] in the treatment of the anuria of mercurial nephrosis may readily be applied in these cases; to furnish adequate fluids (as physiologic saline) to provide a large urinary volume; to provide adequate nourishment to prevent starvation acidosis. Hypertonic glucose (50 c.c. of 50 per cent glucose) was given my patient intravenously twice daily for four days, together with 2000 c.c. of physiologic saline, parenterally. Then 4 grams daily of sodium chloride and 1500 c.c. of fluids were given orally, during the period of increasing edema. Diuresis was established on the eleventh day. No difficulty was encountered in maintaining an adequate carbohydrate and protein intake.

Summary

A case of hemolytic reaction following blood transfusion has been presented. The blood grouping and cross-matching before transfusion were carefully checked and found to be correct after transfusion. While both belonged to group A, with properties MN, the donor belonged to sub-group A_1 and the recipient to sub-group A_2.

This case is another of those rare instances of in vivo incompatibility which could not have been prevented by any of the present in vitro tests.

The basis of treatment in this case was to establish an alkaline diuresis and maintain an adequate carbohydrate and protein intake.

Note: Since this case report was submitted, the patient was examined at regular intervals. Her recovery has been complete.

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ANEURYSM OF THE AORTA WITH COMPRESSION OF THE SPINAL CORD; TWO CASE REPORTS AND REVIEW OF LITERATURE*

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COMPRESSION of the spinal cord is a rare complication of syphilitic aortic aneurysm. Of the thousands of cases of aortic aneurysm that occur in the literature, only 44 present this syndrome. Laennec [1] in 1825 first described the clinical and the necropsy findings in a 36 year old man. In a thorough dissertation of the subject, Goldschmidt-Haas [2] in 1913 gathered and analyzed 32 cases. Gregory [3] in 1934 was able to assemble nine more, and three additional articles have appeared.[4]

The following two cases are presented because of the rarity of the condition. The 15 year survival in the first patient is unique, and the unilateral cord compression manifestations in the second patient are unusual.

CASE REPORTS

Case 1. J. B., a 35-year-old negro ship-worker, was seen first on September 19, 1921, in the out-patient clinic of John Sealy Hospital. He complained of sharp, intermittent pain in the left side of his body, extending from the precordial to the lumbar region, of about a year's duration. The family history was irrelevant. He had married at the age of 18, and his wife had three still-births and a child that lived for 10 months; his second wife, when he was 32, bore a child that died when two months old. Physical examination at this time was normal except for a penile scar and a blood pressure of 145 mm. of mercury systolic and 105 diastolic. The blood Wassermann test was negative, but in October of the same year it was one plus.

The patient was in the hospital from June 9 to July 24, 1922 because of pain across the back and the left side of the chest, especially just beneath the left scapular angle; and because of tenderness to pressure along the sixth and seventh thoracic vertebrae, which he attributed to being hit by a crane a few days previously while working on a ship. There was an accentuated pulsation of the large vessels of the neck, and a faint systolic murmur at the aortic area. The remainder of the examination was negative; the patellar reflexes were normal and the Romberg test was negative. The urine had a faint trace of albumin and some hyaline and granular casts. Two Wassermann tests were reported three and one plus respectively. Roentgenographs of the chest showed no evidences of fracture, but there was an aneurysm of the transverse and the descending portions of the aortic arch, measuring 15 cm. in length, 10 cm. in width and 14.4 cm. transversely; the aorta was 10 cm. wide. No erosion of the vertebrae was noted. No treatment other than that for symptomatic relief was administered.

He returned to the clinic in September and October of 1922, stating that for several weeks he had had weakness of both legs and numbness of both feet. The patellar and achilles reflexes were found to be definitely exaggerated and the Romberg was positive. He was referred to the dermatology department, and although

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the record of the antisyphilitic therapy was missing, the patient was certain (in 1937) that at this time he received eight intravenous and 16 buttock injections at weekly intervals.

He was not seen again until April 19, 1926, when he was hospitalized until June 15, 1926. He had had to quit working because of the pain in the left side, which now was boring and constant in character. He had numbness of both feet, so that he could not sense on what he was walking, and weakness of his legs, requiring the use of a cane. Four months previously he had noted that lying down on the left side would make him cough and would produce a sensation of weight in his chest; the cough did not accentuate the back pain. A month before he had begun to have intermittent urinary incontinence. He had no dyspnea, dependent edema or other significant symptoms.

On physical examination, the heart was enlarged, measuring 10 cm. to the left of the midline, and there was a soft systolic murmur at the aortic area; the blood pressure in both arms was 120 systolic and 80 diastolic. The lungs were clear. The upper part of the body showed no neurological abnormalities. At the level of the seventh thoracic segment he was hyperesthetic to pin prick, and below that level sensation was reduced to pain, touch, heat and cold. The abdominal and cremasteric reflexes were absent. The patellar reflexes were equal and exaggerated, the Babinski sign was positive bilaterally, and there was clonus of both ankles. He could not stand without support and was recorded as being incontinent.

The urine was negative except for occasional faint traces of albumin. The red blood cell count was 4,200,000 with 70 per cent hemoglobin, and the white cell count was 6,000 with 61 per cent polymorphonuclears. The Wassermann test of the blood was negative. The cerebrospinal fluid was clear and colorless, with 10 lymphocytes, normal reducing properties, increase in the quantity of globulin, a negative Wassermann and a colloidal gold curve of 0000000000.

Fluoroscopy and roentgenography of the chest showed the left halves of the third, fourth, fifth and sixth thoracic vertebrae to be entirely destroyed by a large, round mass in the left chest, which also produced pressure and erosion of the posterior portions of the sixth and seventh ribs. The mass was continuous with the aortic shadow and of the same density as the heart; it was expansile and "in all probabilities an aneurysm of the aortic arch."

The next admission to the hospital was from April 14, 1927, to February 12, 1928. There were no significant changes in the history or the clinical findings except for some progression of the condition. The legs were spastic and he could walk only a few yards with the aid of crutches; he was incontinent. The level of hypesthesia remained at the seventh thoracic segment. The Wassermann test of the blood was negative, and the results of two examinations of the cerebrospinal fluid were the same as those obtained on previous study. Roentgenographs showed no increase in the erosion of the spine or in the size of the aneurysm.

A follow-up note in October 1928, stated that the patient was feeling well except for some pain in the back, and that he was confined to a wheel-chair.

Nine years later, in September 1937, he was seen in the streets of Galveston, propelling himself in a hand-driven wheel-chair, and was asked to reënter the hospital. Except for the pain in the back, still present on the left side, extending from the left scapula to the left groin, and the pain in the soles of both feet of the paraplegic legs, he felt well. He was incontinent, but could predict the times of his defecations and micturitions, and rarely soiled himself. He felt cold and dead from the waist down, but had had no trophic ulcers. He had no cough, dyspnea or precordial pain, although anger sometimes precipitated an uncomfortable cardiac palpitation and "heaviness in the chest." Constipation was troublesome, but his appetite was excellent and he had gained about 10 pounds in weight.

Physical examination at this time showed a negro, 51 years of age; he looked well except for the moderate atrophy of the lower extremities. His weight was about 200 pounds, and his height six feet. The temperature and the respiratory rate were normal, and the pulse rate 90 per minute. The head was normal except for some dental caries and the presence of arcus senilis; the pupils were small, regular and reacted to light and accommodation. The fundi were normal. There was a slight tracheal tug, and slight suprasternal pulsation. The left side of the chest appeared fuller than the right anteriorly, and a pulsation synchronous with the heart could be felt on firm pressure just to the left of the fifth thoracic vertebra. The left chest was dull to percussion and the breath and voice sounds were hardly audible except at the base posteriorly; the right lung was normal. The heart was enlarged, measuring 11 cm. to the left of the midline; the sounds were normal, with a soft systolic murmur at the aortic area. The blood pressure was 144 systolic and 110 diastolic in both arms; it could not be obtained in the lower extremities, where the pulse also was absent. The arms were normal; the fingers were not clubbed. The abdomen was obese and normal. The back was stiff and tender to pressure on the fourth to the seventh thoracic vertebrae; no masses or deformities were visible. There was moderate atrophy of the musculature of the lower extremities and well-developed foot-drop. The skin below the seventh thoracic segment was drier and less resilient to the pinch than the integument above the level. This was also the line for marked hypesthesia to pin-prick and anesthesia to light touch. He could move the toes slightly and was able to contract feebly the adductor muscles of the thigh. The legs were flaccid, but the patellar and achilles reflexes were markedly exaggerated, there were bilateral Babinsky, Gordon and Oppenheim signs, and sustained clonus of the ankles and the knees. The abdominal and the cremasteric reflexes were not elicited. The sense of position was present in the toes, and the vibratory sense was not impaired.

Urine examinations were negative; there were occasional pus cells in the sediment. The red blood cell counts ranged about 5,000,000 with 90 per cent hemoglobin, and the white counts about 9,000 with 70 per cent polymorphonuclears. The blood Wassermann and Eagle tests were negative. The sedimentation rate was 26 mm. in one hour. The blood urea was 22.4 mg. per cent and the non-protein nitrogen was 45.6 mg. per cent.

The electrocardiogram showed sinus tachycardia and sinus arrhythmia, ventricular premature contractions and left axis deviation (figure 1).

Fluoroscopic and roentgenographic studies indicated a massive aneurysm of the transverse and descending portions of the aortic arch. The mass measured 13.5 cm. in the transverse diameter and 13.5 cm. in the vertical and antero-posterior planes. There was extensive erosion of the fifth, sixth and seventh ribs and the third to the seventh thoracic vertebrae on the left side. The erosion of the spine in the two middle vertebrae extended approximately two-thirds across the segments, but the destruction on the anterior surfaces was very slight as compared to that on the lateral aspects. The mass was expansile at its lower margins and little if any in the upper and lateral sides, indicating that laminated clots were present; there was calcification just inside the aneurysmal wall in the upper and lateral borders (figure 2 a).

Lumbar puncture revealed the cerebrospinal fluid to be under a pressure of 170 mm. of water, and no rise in this pressure was elicited by jugular compression. There were three lymphocytes per cu. mm., and 45 mg. of protein; the Wassermann test was negative and the colloidal gold curve was 1111233321. Iodized oil injected intrathecally in the lumbar region demonstrated the block at the seventh thoracic segment (figure 2 b).

A day after the last procedure it was noted that the reflexes of the lower extremity were hypoactive, that the clonus had disappeared and that the pathological reflexes could not be demonstrated. These changes disappeared gradually, and five days later the neurological findings returned to the former status.

The patient is doing well, is capable of as much activity as his paralysis will permit, and his morale is excellent. Except for the history of eight intravenous and 16 intramuscular injections in 1923, and a few doses of potassium iodide, he has received no antisyphilitic treatment.

Case 2. F. J. H., a 54-year-old white night-watchman, was admitted to John Sealy Hospital on October 5, 1935, with the complaints of severe pain in the chest of two years' duration; of pain in the low back, left hip and thigh; and of difficulty in urination for 10 months.

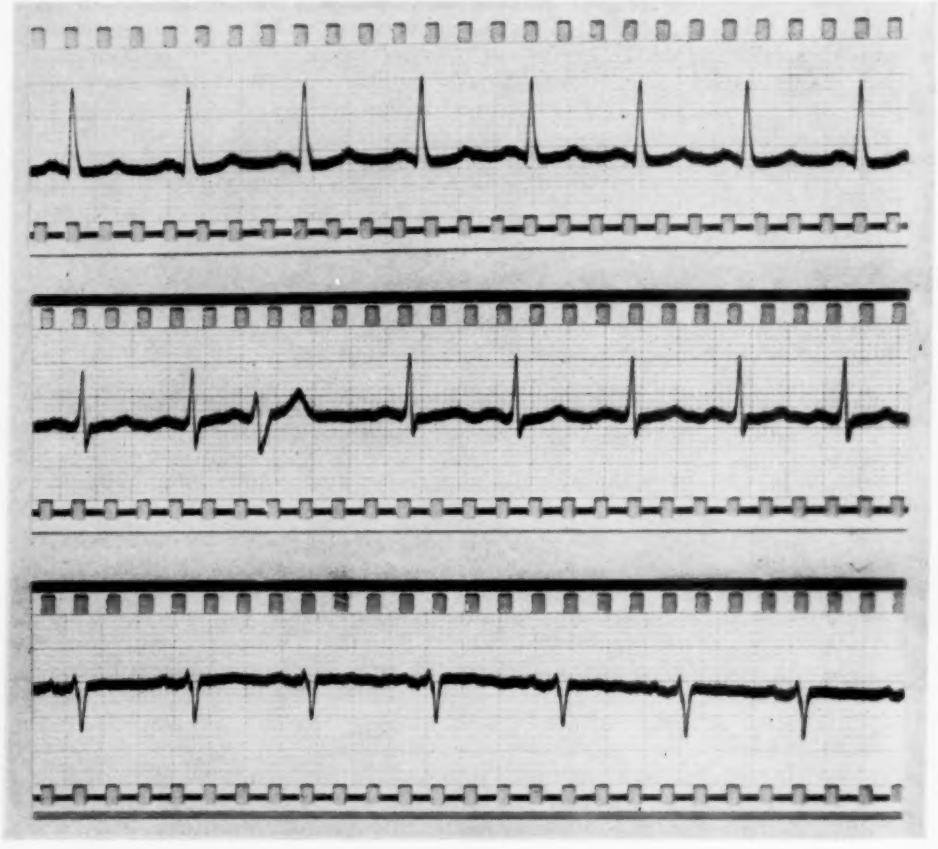

FIG. 1. Electrocardiogram in Case 1.

He had had two previous entries to the hospital. In 1934 he had acute gangrenous appendicitis, and was discharged 20 days post-operatively. In May 1935, he was on the urological service for acute urinary retention. At that time the heart was enlarged to 10.5 cm. to the left of the midline, the second aortic sound was accentuated and of tambour quality, and the blood pressure was 140 systolic and 90 diastolic. He had generalized abdominal pain and tenderness, with radiation down the thighs and into the scrotum. The urine was normal, the red blood cell count was 4,250,000 with 85 per cent hemoglobin, and the white blood cell count was 8,400 with 7.9 per cent polymorphonuclears. Cystoscopy revealed hypertrophy and trabecula-

tion of the bladder and prostatic enlargement. He was discharged with the diagnoses of chronic prostatitis and arteriosclerotic heart disease.

The man admitted a penile sore in 1915. He stated that he had noted some dyspnea on exertion since an attack of pneumonia in 1927. In 1932 he had begun to have intermittent attacks of severe pain in the left side of the chest, sharp and shooting in character, accentuated with deep respirations and on coughing, and located just under the breast but with occasional radiation to the right lower chest and back.

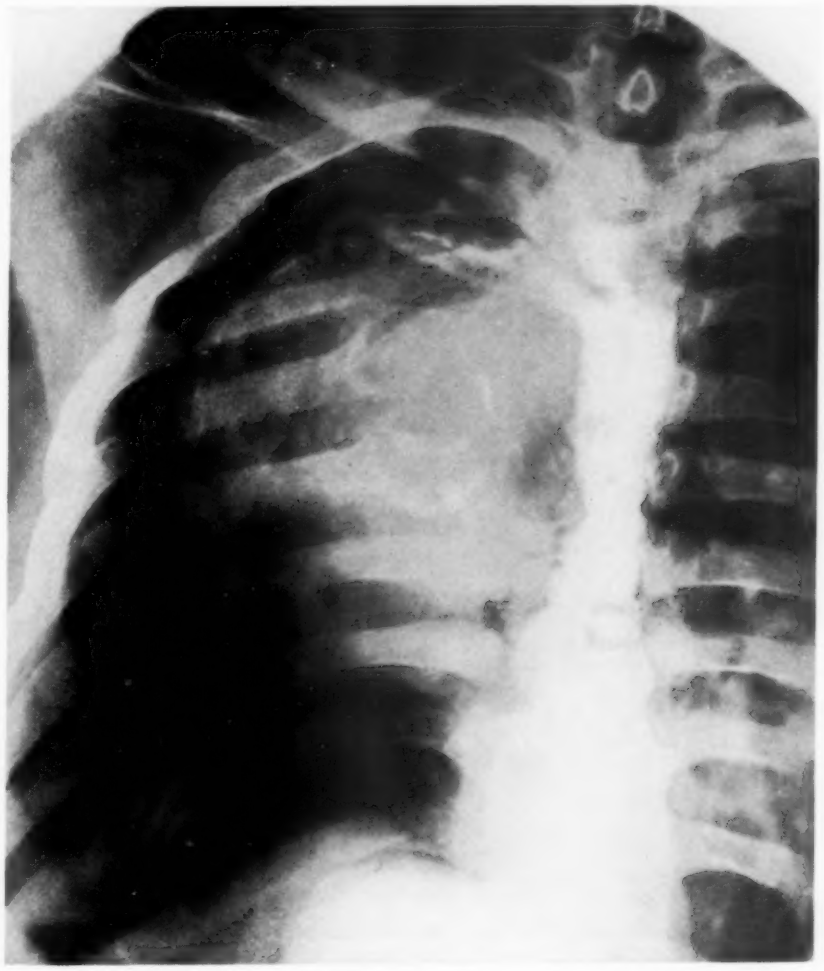

FIG. 2. a. Roentgenograph in Case 1, showing aneurysm and vertebral erosion.

During the previous two years his dyspnea had progressed so that he could walk only two blocks without resting. In January 1935, he began to notice difficulty in initiating micturition, and some dribbling of urine. He also began to have pain in the lumbar region of the back, which radiated to the left thigh and hip. At first this pain was paroxysmal, throbbing and "like a toothache;" it became progressively worse and finally constant, and during the two preceding weeks had involved the left lower portion of the abdomen.

The family history was irrelevant; he had six apparently healthy children. The past history was not significant except for a gradual loss of 70 pounds in weight and a resultant loss of strength during the preceding year.

Physical examination showed an elderly, emaciated man, weighing 110 pounds. The temperature was 99° F., the pulse rate was 85 per minute and the respiratory rate 22 per minute. The cervical, inguinal and epitrochlear lymph nodes were palpable. The left eye was almost blind because of an old traumatic corneal ulcer; the right

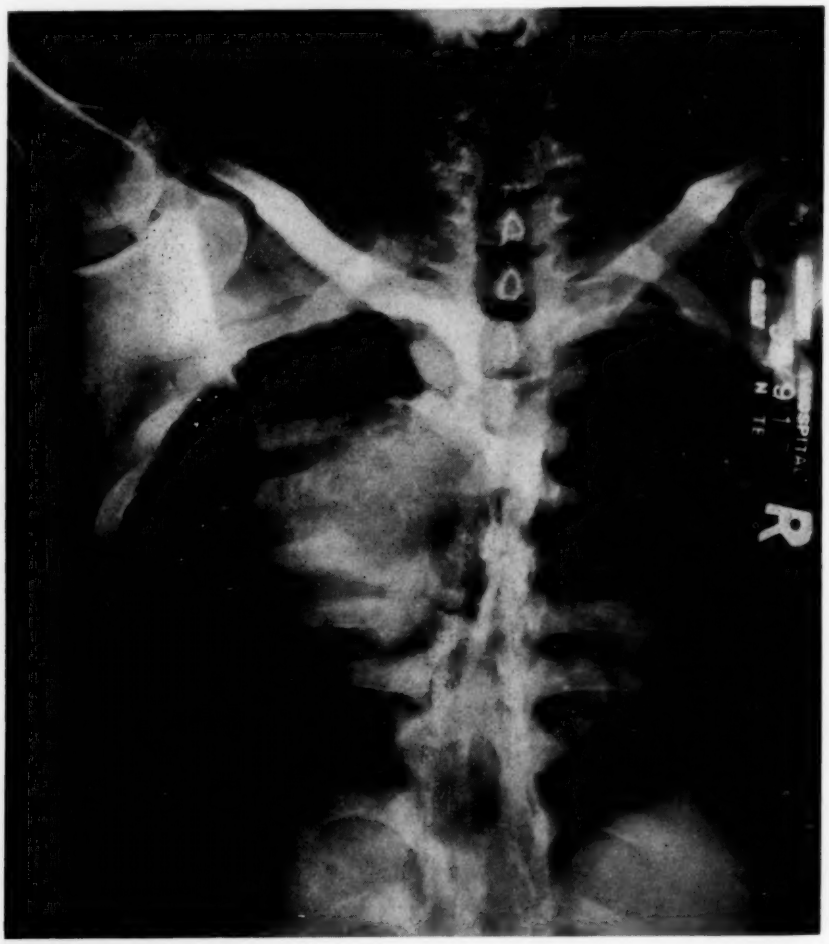

FIG. 2. b. Roentgenograph in Case 1, showing block of intrathecal iodized oil.

pupil was small, irregular and reacted sluggishly to light. The fundi were normal. There was impaired resonance at the base of the left lung posteriorly, and a few moist râles were heard in that area. The heart was enlarged to 11 cm. to the left of the midline. The rate and rhythm were normal, there were systolic murmurs at the aortic and mitral areas, and a markedly accentuated second aortic sound; the blood pressure was 134 systolic and 74 diastolic in both arms. Examination of the abdomen revealed a visible pulsation on the left side, and a pulsating mass was felt in the left upper quadrant, which was thought to be an aneurysm of the abdominal aorta. He was

tender to pressure on the abdomen and had slight rigidity of the upper abdominal muscles. The left elbow was ankylosed from an old injury. The left leg felt much warmer than the right, but there was no edema, and the peripheral pulses were good and equal in both lower extremities.

He swayed to the left on walking. The left gluteal muscles were atrophied, and the muscle power of the left leg was decreased. The achilles reflex was absent on the left and present on the right, but the other deep reflexes were normal; there was a suggestive Babinsky sign on the left side. Hypesthesia to pain and pressure was detected on the left side below the sixth thoracic segment; sensation on the right side of the body was normal. Rectal examination revealed relaxation of the anal sphincter and an enlarged prostate. He was noted to be incontinent.

The urine had a slight trace of albumin, many red blood cells and a few pus cells. The red blood count was 3,600,000 with 60 per cent hemoglobin, and the white blood cell count varied between 7,600 and 13,000, with about 80 per cent polymorphonuclears. The Wassermann test was two plus and the Eagle test was positive. Nonprotein nitrogen of the blood was 28.5 mg. per cent, and the urea nitrogen 17.1 mg. per cent a few days after admission.

Lumbar puncture was performed on October 11, 1935; the fluid was clear, with 10 mg. of protein and no cells, with a negative Wassermann test and a colloidal gold curve of 1232100000. The initial pressure was 320 mm. of water, with a prompt rise to 560 mm. and a prompt fall to 320 mm. of water upon jugular compression. Seven days later, the fluid was clear, with 19 mg. of protein, normal reducing properties, 1 lymphocyte, anticomplementary Wassermann test and a colloidal gold curve of 1223100000.

Antero-posterior and lateral roentgenographs of the lower spine visualized extensive destruction of the thoracic eleventh and twelfth and the lumbar first and second vertebrae; the erosion was principally on the anterior aspect, but also involved the left sides of the bones. It was interpreted as being due to an aneurysm of the abdominal aorta.

The patient's course in the hospital was steadily down-hill. He had occasional elevations of temperature up to 102° F., a pulse rate of 80 to 100 per minute and a normal respiratory rate. The pain in the lumbar region of the back and the left leg became progressively worse.

Examination of the chest on November 11, 1935, revealed decreased expansion of the left side, dullness on percussion, absent tactile fremitus, absent breath sounds and no transmission of the spoken voice; the heart was displaced to the right and Grocco's triangle was made out posteriorly on the right side. Roentgenographs of the chest showed dense opacity of the left chest and displacement of the heart shadow, indicative of massive effusion. Five hundred cubic centimeters of bloody fluid were aspirated; the specific gravity of the fluid was 1.027; and numerous red blood cells, 1,300 leukocytes and no organisms were found microscopically. Another 500 c.c. of blood were removed from the left pleural cavity on November 18, 1935, but the fluid reaccumulated rapidly and no further thoracocenteses were done.

Early in December slight pitting edema of the ankles was observed, and there was transient swelling of the left, and then of the right, arm. On December 14, the left leg was completely anesthetic, the deep reflexes were absent and the Babinsky sign was positive; the right leg was normal. The breath was markedly uriniferous in odor, the heart sounds were rapid and of poor quality, and the right lung base contained moist râles; the left pleural cavity had the physical signs of massive effusion. The patient continued to have pain in the left chest, swelling of the left arm and some difficulty in swallowing. On January 3, 1936, he began to vomit, gradually became stuporous, and expired on January 6, 1936.

Treatment had been directed chiefly towards the relief of pain; potassium iodide, up to 0.3 gm. three times a day, was given, and between November 23 and

December 14, 1935, he received 19 doses of mercury succinamide, 0.01 gm. intramuscularly.

Necropsy. Necropsy was performed 36 hours after death.

The left pleural cavity contained about 1200 c.c. of blood, much of it in the form of fairly firm clots, and in the right chest there were about 150 c.c. of bloody fluid. The pericardial and the peritoneal cavities were normal. The heart weighed 380 gm., and was normal except for hypertrophy of the left ventricle; the aortic valves were normal.

The ascending aorta measured 6 cm. in the internal diameter; the intima had many small yellow plaques and tree-bark striations. Just at the origin of the left subclavian artery the aorta was dilated to 17 cm. in diameter; this dilatation extended fairly evenly down to the second lumbar segment: the greatest diameter of 20 cm. was at the seventh thoracic region and there were constrictions to 15 cm. at the fifth thoracic and at the diaphragmatic opening. In the middle of this tri-lobar aortic dilatation, on the posterior aspect, was an oval aneurysmal sac, measuring 7 cm. in the vertical and 3.5 cm. in the horizontal planes, and lying opposite the seventh and portions of the sixth and eighth thoracic vertebrae. There was some erosion of the vertebrae on the anterior and left lateral aspects of the fifth thoracic to the second lumbar segments, but the oval sacculation had destroyed the anterior and the left lateral surfaces of the bones and produced direct pressure on the cord at the level of the sixth to the eighth thoracic vertebrae. The wall of the aneurysm adhered firmly to the bone and the dura, and around the attachment to the vertebral bodies leakage of blood had occurred, with extension of blood into the left pleural cavity and the left retroperitoneal region. No definite rupture of the aorta was found. There was no blood around the spinal cord, and the spine had no pathological fracture. The wall of the whole descending aorta, especially on the posterior surface at the level of the fifth to the eighth thoracic vertebrae, was thin and the layers of the vessel wall were indistinguishable. The intima contained many soft yellow plaques and vertical tree-bark striations.

The remainder of the findings were not significant. There was congestion of the liver and the lungs, the mucosa of the bladder was red and injected, and the prostate was enlarged.

Microscopic sections of the aorta showed perivascular infiltration by lymphocytes and changes in the wall diagnostic of syphilis. The arterioles and the arteries of the kidneys were thickened, and the bladder was chronically inflamed. Unfortunately, no detailed studies were made of the spinal cord.

Discussion

All of the aneurysms of the aorta producing spinal cord compression reported in the literature, as far as can be determined from the clinical, the serological or the pathological findings, were of syphilitic origin. In view of the frequency in which aortic aneurysms erode the vertebrae, the occurrence of spinal cord involvement is rare. Lucke and Rea,[5] in a study of 249 subjects, tabulated such erosion in 53, and spinal cord compression only in one. An analysis of 100 aneurysms at John Sealy Hospital[6] showed that over a quarter erode the vertebrae to some degree; yet of 170 aneurysms only one involved the cord (Case 2).

The pathological process is that of gradual pressure-erosion of the contiguous structures by a large, long-standing aneurysmal tumor. Any portion of the aorta may be involved, although in the great majority of cases the aneurysm naturally arose in the descending thoracic aorta; in 44 cases the locations were distributed as follows: 33 in the descending thoracic aorta, six at the arch, four in the ab-

dominal and one in the ascending portion. The condition prior to actual cord compression is illustrated by eight cases collected by Goldschmidt-Haas [2] in which the aneurysm eroded an opening into the vertebral canal without actually involving the cord. The compression and the resultant peripheral symptoms may be due to any one of the three occurrences: the aneurysm may produce direct pressure on the cord; an epidural hemorrhage due to rupture of the aneurysmal sac may result; or the weakened bone structure may collapse and pinch off the cord. It is interesting that although cases of marked adhesion between the dura and the aneurysmal wall are reported, in no instance was the dura penetrated. The changes in the cord were secondary to pressure, and the pathological studies in cases with paraplegia varied from lack of grossly or microscopically demonstrable damage [7] to evidence of complete transverse myelitis. Concomitant neurosyphilitic involvement, such as tabes dorsalis [8] also has been described.

Many more males than females were reported with this syndrome; of 39 cases, only six were women. The youngest patient recorded was 30 years of age, and the oldest 79; the age distribution was as follows: third decade, 12; fourth decade, nine; fifth decade, 15; older, three. However, of the 26 cases occurring prior to 1913, 11 were in the third decade of life, whereas only one of the 13 subsequent cases was under 40 years of age. Antisyphilitic treatment was lacking or inadequate in all patients.

In the majority of cases in which the clinical history was given, symptoms of aneurysm—such as pain in the chest, dyspnea or cough—were present, often of several years' duration, before the manifestations of spinal cord involvement. The onset of the cord symptoms usually was gradual (in 22 of Goldschmidt-Haas' 32 cases), but sometimes was very sudden, especially when due to epidural hemorrhage or to pathological fracture of the spine.

Physical examination of the patients often revealed syphilitic stigmata, aortic regurgitation, or the classical signs of aneurysm. Pulsating tumors or deformity of the spine [4b] occasionally were encountered. The paraplegia differed in no respects from paraplegia due to other causes. In most instances the process was not complete and was spastic in type (Case 1). Preëxisting neurosyphilis confused the picture in several patients.[8] Unilateral involvement occurred (Case 2); and a Brown-Sequard syndrome was present in one patient.[9]

The variability in the results of the serological tests for syphilis in these patients is well illustrated in Case 1. Negative Wassermann tests were not uncommon.[10] In the cerebrospinal fluid, the cell count and the protein varied from normal to moderately elevated, and with epidural hemorrhage the fluid was blood-tinged; Froin's syndrome was reported,[11] but not consistently. In the more recent cases, spinal block was demonstrated by the hydrodynamics, either by jugular compression or by combined cisternal-lumbar puncture,[3] or by the intrathecal introduction of iodized oil. The fluid was normal in all respects in one patient,[12] but the block at the fourth thoracic segment was demonstrated by the latter method. As in Case 2, the involvement may not be sufficiently advanced to produce spinal canal block. Alterations in the fluid due to neurosyphilis also were found in several cases.

Roentgenographs cannot fail to show the large aneurysms and the marked destruction of the vertebrae in these cases; however, the importance of fluoro-

scopy must be stressed in the differentiation of aneurysms from other thoracic or abdominal tumors, such as neoplasms, echinococcus cysts and dermoids.

The diagnosis is based on the clinical picture of aneurysm, on the presence of paraplegia, and on the roentgenographic substantiation. The most important condition that enters into the differential diagnosis is cord tumor; a complete clinical and roentgenographical study should eliminate the possible confusion. It has been alluded to above that other tumors may erode the vertebrae and possibly cause compression of the cord. Paraplegia in a syphilitic may be due to a specific meningo-myelitis.[13] Dissecting aneurysm of the aorta may produce neurological phenomena secondary to the disturbances in the blood supply to the cord.[14] Furthermore, radicular symptoms are not infrequent in saccular aneurysms of the aorta, and may be mistaken for true spinal cord compression. For example, a 40-year-old negro, who died at John Sealy Hospital in July 1935, came in with pain, tenderness and rigidity of the abdomen; on operation a liter of blood was found, and ruptured aortic aneurysm was suspected. The man developed anesthesia and paralysis of the right leg two days before exitus, and roentgenographs revealed erosion of the first and second lumbar vertebrae. On necropsy there was a large ruptured aneurysm 9 cm. above the bifurcation of the aorta, with erosion of the first and second lumbar vertebrae, but no penetration into the spinal canal.

Treatment of patients with cord compression due to aortic aneurysm must be directed towards the preservation of the weakened bony framework by bed rest and applicable splinting. Laminectomy was tried in one instance,[15] with the predictable results. In regard to antisyphilitic therapy, Gregory's statement [3] that it "has been consistently unsuccessful" in these cases is not surprising considering the advanced nature of the process. Such treatment must be carried out with extreme care; the danger of the initial use of arsenicals is illustrated strikingly by one patient who died 10 hours after the injection of 0.15 gm. of neoarsphenamine.[11] As in other aneurysms of syphilitic etiology, gradually increased doses of heavy metals (e.g., bismuth salicylate, up to 0.1 gm.), weekly over a two to three month period, must be administered before starting neoarsphenamine, the initial injections of which should be in 0.025 to 0.05 gm. doses, gradually advanced to 0.3 gm. Arsenicals should be employed in courses of from 10 to 12 injections alternating between succeeding courses of bismuth or mercury. Potassium iodide may accompany this routine. "Thereafter, much will depend on the symptoms and on the response to treatment." [16]

The course and the prognosis of all aortic aneurysms are extremely variable. The majority of the patients die within a two-year period, but Cole and his coworkers [16] write that "the average duration of life after detection of aneurysm of patients who had only an inadequate treatment was 37 months, which increased to 75 months when adequate antisyphilitic treatment was given." Longevity is not rare, and survival with aortic aneurysm for as long as 29 years has been reported.[17] The duration of life in patients with spinal cord compression due to aortic aneurysm, from the first symptoms of aneurysm until death, was most often from two to three years, but a fatal outcome was usual within a few months —or acutely—after the onset of spinal cord involvement. The presence of the syndrome for 15 years (Case 1) is by far the longest on record.

SUMMARY

1. Two reports are presented of syphilitic aneurysm of the aorta with erosion of the vertebrae and compression of the spinal cord; one patient has survived the condition for 15 years.

2. The clinical and the pathological findings, the treatment and the prognosis in aortic aneurysm with spinal cord compression, based on the review of 46 recorded cases, are discussed.

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EDITORIAL

SYNTHETIC ESTROGENS

The remarkable advances in the field of the chemotherapy of infectious diseases during the past two years have served somewhat to obscure the hardly less remarkable achievements, chiefly of English workers, in the field of synthetic substitutes for the female sex hormones. The essential point is the establishment of the fact that estrogenic activity is not exclusively a property of compounds structurally similar to the natural hormones, that is, possessing the phenanthrene nucleus. In a series of brilliant papers, Dodds and his co-workers at the Courtauld Institute in London have described a number of simpler substances having estrogenic properties and in some cases of even greater activity than the naturally occurring hormones or their derivatives.

The story of this discovery furnishes an example of an important advance which has emerged out of efforts originally directed toward quite a different goal, namely, the investigation of the possible relation between chemical structure and physiological action of carcinogenic agents. In 1933, Cook and Dodds, and their co-workers, described synthetic phenanthrene derivatives having estrogenic properties. They found many, including ergosterol and calciferol, as well as several which were also active carcinogens. Three years later (1936) Dodds reported a series of compounds, also active, which did not possess this phenanthrene condensed-ring structure. A certain degree of unsaturation appeared to be requisite, especially ethylenic bonds. Just two years ago Dodds made the announcement that a comparatively simple compound, anol, or *p*-hydroxy propenyl benzene, possessed a very high degree of estrogenic activity, although shortly afterwards he reported that the activity was not due to anol itself but to another substance separating from the mother liquor. It now seems quite clear that there are a number of active compounds which may be looked upon as simple condensation derivatives of anol, and related to stilbene. The most promising of these new synthetic compounds is 4:4′ dihydroxy $\alpha\ \beta$ diethyl stilbene, which Dodds has named stilboestrol. Stilboestrol appears to possess many, if not most, of the physiological and clinical properties of the natural hormone. Estrone effects in rodents have now been reported on the vagina, uterus, breasts, anterior pituitary, male sex organs, and on the sex behavior. Oral administration interrupts early pregnancy in rabbits. Recent clinical studies show that the compound may produce an estrone effect on the hypoplastic uterus. It will restore the normal functioning appearance to the atrophic (climacteric) vulva and vagina, may induce painful swelling of the breast, and will relieve in many cases the pain of dysmenorrhea. The restoration of genuine menstruation has also been reported in a castrate woman by the use of stilboestrol followed by progesterone. The two interesting thera-

peutic uses of the estrogens not directly related to sex function which have been found recently, namely, in the gonorrheal vaginitis of childhood and the relief of atrophic rhinitis, also seem to be equally influenced.

As Dodds and his co-workers have pointed out, the formula of stilboestrol can be written so that it has a resemblance to that of estrone but without the ring structure. The suggestion therefore arises as to whether stilboesterol, or a closely related compound, may represent either a building stone or a decomposition product of the naturally occurring estrogen. Since synthetic stilboestrol is active in ovariectomized animals, the possibility that it represents a breakdown product seems unlikely. It is remarkable indeed that such complicated physiological transformations can be brought about by such rather simple compounds.

The stilbene derivatives are not the only compounds with estrogenic action which have recently been studied. Robson and his co-workers at Edinburgh over a year ago described triphenyl ethylene, 10 mg. of which produced the typical estrus activity, including mating, in rodents for a continuous period of eight or nine weeks. When large subcutaneous doses of a closely related compound, triphenyl chlor-ethylene, were tested a more prolonged action resulted, in equivalent doses, than is obtained with the best of the estrogenic compounds in common use.

Recently there has been great interest, especially in England and in Germany, in the clinical possibilities of these new compounds, and particularly of stilboestrol and its simple derivatives. These can be rather easily prepared, and a rather extensive study, both on the Continent and by the Therapeutic Trials Committee of the Medical Research Council in England, seems to indicate their essential lack of toxicity. Certain side reactions, however, most serious of which are the occasional occurrence of rather severe nausea and vomiting, make it imperative that they be introduced into clinical use with great caution.

Of interest for future work is the possibility that this successful production of synthetic compounds with estrogenic activity may point the way to a search for substitutes for other hormones which also possess the phenanthrene grouping, such as progesterone, testosterone, and the cortical hormone. Although many theoretical objections may be proposed against the probable successful outcome of such efforts, the possibilities nevertheless remain and will no doubt be carefully explored.

G. H.

Erratum. In Dr. Frederick M. Allen's article on "Tolerance and Toxicity of Insulin. II. With Forced Administration of Carbohydrate," February 1939 ANNALS, page 1271, the first sentence of the last paragraph should read: "The 14 kg. animal depicted in figure 2 survived an insulin dose of 2,000 units (in the *Physiatric* Institute)."

REVIEWS

Spinal Anesthesia. By Louis H. Maxson, A.B., M.D., Practicing Specialist in Anesthetics; Former Chief Anesthetist, Harborview (King County) Hospital, Seattle, Washington; with a foreword by W. Wayne Babcock, M.D., LL.D., F.A.C.S., Professor of Surgery, Temple University School of Medicine. 409 pages; 16 × 23.5 cm. J. B. Lippincott Company, Philadelphia. 1938. Price, $6.50.

Spinal anesthesia is a form of regional anesthesia, applicable to a relatively large portion of the body. Although it was discovered by Bier, a German, the method was first popularized by Tuffier and Reclus, two Frenchmen. In 1898, Bier had the temerity to have 2 c.c. of a 1 per cent cocaine solution (20 mg.) injected into his own spinal canal to observe its effects. Following this successful experiment, Bier administered a similar dose to his assistant, Schmeiden. In 1899, he reported six operations under low spinal anesthesia. Tait and Coglieri of San Francisco, apparently were the first surgeons in this country to make use of this method of anesthesia. Since Bier's discovery, there have been alternating waves of popularity and distrust of this method of anesthesia. George P. Pitkin probably stimulated the most widespread interest (1927) in spinal anesthesia and established it on a sound basis.

The author gives a detailed anatomical description of the vertebral column and spinal cord relationship. The influence of position on curve is considered. There is an excellent description of the autonomic or vegetative nervous system with its physiological divisions; and full data on the cerebro-spinal fluid.

The variables of spinal anesthesia are discussed. The various drugs which have been employed and their relative merits are dealt with. Pre-anesthetic medications are reviewed.

A chapter is devoted to technical considerations and another to technical difficulties with a review of typical technics from 1902 (Le Filliatre) to 1934 (Vehrs). The newer preparations are discussed, e.g. pontocaine, nupercaine, spinocaine, etc.

The effects of spinal anesthesia are described, both immediate and delayed. The causes of failures are considered, along with the difficulties, dangers and mortality. Complications and sequelae are discussed in detail. Space is devoted to comparison of the advantages and disadvantages of this method of anesthesia. Indications and contraindications are carefully evaluated.

A chapter is devoted to miscellaneous indications for spinal anesthesia, such as intestinal obstruction (diagnosis), temperature studies of the lower extremities, megacolon, etc. Spinal anesthesia, in various surgical specialties, is discussed.

A very extensive bibliography is given in addition to a very satisfactory subject index.

The book is extremely comprehensive in its scope and is a very valuable contribution to the literature on this subject. It should be of inestimable value to the anesthetist, the student and to individuals interested in the question of spinal anesthesia.

G. H. Y.

The Primate Thalamus. By A. Earl Walker, M.D., Instructor in Neurosurgery, The University of Chicago. 321 pages; 15.5 × 23.5 cm. The University of Chicago Press, Chicago, Illinois. 1938. Price, $3.00.

The present volume is an excellent discussion of the anatomy and physiology of the thalamus of the macaque. It begins with an historical introduction which, though

brief, brings the material well up to date. The second chapter describes Walker's method of study and experimental material including a brief review of the Nissl and Marchi technics. The author devotes the third chapter to a description of the gross and nuclear structure of the macaque thalamus. The remainder of the book, four substantial chapters, includes: (*a*) a description of the afferent connections of the thalamus; (*b*) a discussion of the relation of the thalamus to the cerebral cortex; (*c*) a rather short consideration of the relation of the geniculate bodies to the cerebral cortex; (*d*) an excellent summary of the anatomical, physiological and clinical significance of the thalamic region of the brain. When the author discusses the connections of the thalamus, he is at his best. He has consulted all of the literature dealing with each one of the known connections and has verified these connections in the macaque brain by means of ablation of parts of the brain and the study of degeneration of the connections. By these means he has been able to verify some opinions and to act as referee in cases where there is a disagreement. Unfortunately, as a general rule, he only cites one experimental case of his own to show the connections but it is to be presumed, since these experiments lasted over a period of six years, that each experiment has been verified by other similar operations. An attempt to discern the damage to the nuclei and their connections is the primary purpose of each of these experiments but there is a description of the behavior of the animal which is also of value in showing the physiological picture. The gross areas of the brain affected are shown by drawings of the whole brain as well as of sample serial sections showing the local damage. There is, of course, little discussion of the possible emotional function of the thalamus.

The book is a decided contribution to our knowledge of the anatomical connections and the physiological significance of this little-known part of the nervous system, as well it should be, since the work was done under the direction of Percival Bailey, John F. Fulton and Bernardus Brouwer.

L. S. S.

Diabetes Insipidus. By C. FISHER, W. R. INGRAM, and S. W. RANSON. 212 pages; 21 × 28 cm. Edwards Brothers, Inc., Ann Arbor, Michigan. 1938. Price, $5.00.

The exact anatomical location of lesions which will cause diabetes insipidus has long been a controversial matter from both a clinical and experimental viewpoint. The excellent work of Fisher, Ingram, and Ranson definitely localizes such lesions to the supra-optic-hypophyseal system. The authors further demonstrate that the symptoms of permanent polyuria and polydipsia will not appear unless there is normal anterior pituitary tissue present. Their experimental work is valuable for its careful histological examinations, the production of localized lesions, and the large series of animals used (cats and monkeys).

In the latter part of the book the authors review the literature and try to fit the conflicting data of other investigators into their conception of diabetes insipidus. From an anatomical standpoint the picture appears to be consistent and logical but a clear-cut analysis of the subject is impossible until some of the physiological mechanisms involved are more completely understood. As Fisher, Ingram, and Ranson indicate in their introduction the reader whose time is limited will find the more important results of their investigation presented in Chapters III, V, X, and XI.

J. H.

The Cerebrospinal Fluid and Its Relation to the Blood; A Physiological and Clinical Study. By SOLOMON KATZENELBOGEN. xix plus 468 pages; 16 × 23.5 cm. The Johns Hopkins Press, Baltimore, Maryland. 1935. Price, $5.00.

The purpose of this book has been to review and analyze the vast material which has accumulated on the cerebrospinal fluid and its relation to the blood. The author has added his own researches to the work of others in an attempt to formulate the actual state of our present knowledge. This purpose has been very well achieved.

The introductory chapters deal with the origin, mode of formation, and circulation of the cerebrospinal fluid. The existing theories are discussed pro and con, and one is impressed that much remains to be done before these fundamental problems are settled. The remaining chapters deal with the physico-chemical constitution of the cerebrospinal fluid in comparison with the blood in both physiological and pathological states. The hemato-encephalitic barrier is fully discussed, and individual chapters deal with the chief chemical constituents of the spinal fluid. The only important omission is the lack of adequate discussion of the total protein content of spinal fluid.

A short chapter is devoted to the important relation of pressure in blood and cerebrospinal fluid. The function of barrier between cerebrospinal fluid and blood is ably discussed, and methods of study of this function are reviewed. The clinical application of artificial alteration of barrier permeability is fully presented.

The book is not a concise guide for clinical study of the cerebrospinal fluid, but is rather a critical reference work on the state of our present knowledge of the cerebrospinal fluid. Both sides of controversial material are presented. The organization of the work is good, each chapter contains a brief summary, and a valuable bibliography is appended. The index is well prepared. The author has made a very valuable contribution and his book is recommended as an excellent reference work.

J. G. A., JR.

The Intellectual Functions of the Frontal Lobes; A Study Based upon Observation of a Man after Partial Bilateral Lobectomy. By RICHARD M. BRICKNER. xvi plus 354 pages; 14.5 × 20 cm. The Macmillan Company, New York. 1936. Price, $3.50.

This monograph is devoted to the study of a patient after partial bilateral frontal lobectomy. In 1930 Dandy removed 116 grams of brain tissue from both frontal lobes in the course of removing a parasagittal meningioma. One year following operation, the patient came under the author's care. During the second postoperative year he was studied carefully by means of formal psychological and neurological tests, as well as by informal continual observation in his daily life.

The literature contains many studies on patients with infections and injuries to the frontal lobe, but this is the first report of a carefully studied patient after partial double frontal lobectomy. The author has summarized his conclusions, and they represent an important contribution to the study of frontal lobe function. There are many factors, however, which enter into the interpretation of functional changes following ablation experiments, so that too much weight cannot be placed on the study of a single case, however carefully it may be done. Symptoms referable to destruction of brain tissue must be differentiated from the positive symptoms which arise as release phenomena from other parts of the intact brain, and herein lies the great difficulty in analyzing ablation experiments, both in animal experiments and in man.

The book contains a brief review of the existing literature on symptoms of frontal lobe injury, a careful presentation of the observations of the patient for more than a year, and several chapters dealing with the interpretation of this study. The monograph is an important contribution, and will be read with interest by the neurologist, psychiatrist, and psychologist.

J. G. A., JR.

COLLEGE NEWS NOTES

New Officers, Regents and Governors

At the General Business Meeting of the American College of Physicians, held on March 30, 1939, in connection with the 23rd Annual Session of the College at New Orleans, Dr. O. H. Perry Pepper, Philadelphia, was inducted as President and the following elections took place:

President-Elect ..... James D. Bruce, Ann Arbor
1st Vice President ..... Allen A. Jones, Buffalo
2nd Vice President ..... Gerald B. Webb, Colorado Springs
3rd Vice President ..... J. Morrison Hutcheson, Richmond

For the term expiring 1942, the following were elected (* reëlected) to the Board of Regents:

Charles T. Stone, Galveston
Reginald Fitz, Boston
*Egerton L. Crispin, Los Angeles
Francis G. Blake, New Haven
William J. Kerr, San Francisco

Dr. Kerr and Dr. Stone served during the past year as President and 3rd Vice President, respectively.

For the term expiring 1942, the following were elected to the Board of Governors:

Oliver C. Melson ..... Arkansas—Little Rock
Ernest H. Falconer ..... Northern California—San Francisco
Fred M. Smith ..... Iowa—Iowa City
Joseph E. Knighton ..... Louisiana—Shreveport
Henry R. Carstens ..... Michigan—Detroit
Edgar van Nuys Allen ..... Minnesota—Rochester
A. Comingo Griffith ..... Missouri—Kansas City
Robert B. Kerr ..... New Hampshire—Manchester
George H. Lathrope ..... New Jersey—Newark
Charles H. Cocke ..... North Carolina—Asheville
Julius O. Arnson ..... North Dakota—Bismarck
Alexander M. Burgess ..... Rhode Island—Providence
Kenneth M. Lynch ..... South Carolina—Charleston
Paul K. French ..... Vermont—Burlington
Walter B. Martin ..... Virginia—Norfolk
Charles E. Watts ..... Washington—Seattle
Walter E. Vest ..... West Virginia—Huntington
Hughs A. Farris ..... Maritime Provinces—St. John, Can.
Charles F. Moffatt ..... Quebec—Montreal, Can.

Dr. Charles H. Turkington, Litchfield, Conn., was elected for the term expiring 1941, succeeding Dr. Francis G. Blake who was elected to the Board of Regents.

Dr. Walter E. Vest, for a number of years Governor for West Virginia and re-elected at the New Orleans Session, has since resigned as Governor because of too great a multiplicity of other duties and responsibilities, and, in accordance with provisions of the Constitution and By-Laws, the President, Dr. O. H. Perry Pepper, has appointed Dr. Albert H. Hoge, of Bluefield, as Governor for West Virginia, to serve until the next regular election.

Cleveland Selected for 1940 Session of the College

At a meeting of the Board of Regents at New Orleans March 31, it was voted to hold the 1940 Session of the American College of Physicians in the City of Cleveland. Announcements will be made later of the appointment of a General Chairman, local committees, and of other details.

Elections to Membership

At the 1939 Convocation of the American College of Physicians at New Orleans, 228 physicians were inducted into Fellowship, representing 39 States, Puerto Rico, 4 Provinces of Canada, the Medical Corps of the U. S. Army, U. S. Navy and the U. S. Public Health Service. The list herewith follows:

William Bluford Adamson ..... Abilene, Tex.
William Wallace Alexander ..... Florence, Ala.
William Hackney Algie ..... Kansas City, Kan.
Ellery George Allen ..... Syracuse, N. Y.
Frederic A. Alling ..... Newark, N. J.
Ellsworth Lyman Amidon ..... Burlington, Vt.
George Edward Anderson ..... Brooklyn, N. Y.
James Brent Anderson ..... M. C., U. S. Army
Russell Sherwood Anderson ..... Erie, Pa.
Fred Ernest Angle ..... Kansas City, Kan.
Kenneth Ellmaker Appel ..... Philadelphia, Pa.
Arthur Graham Asher ..... Kansas City, Mo.
Dudley Curtis Ashton ..... Beckley, W. Va.
John Martin Askey ..... Los Angeles, Calif.

Benjamin May Baker, Jr. ..... Baltimore, Md.
Fred Eugene Ball, Jr. ..... Chicago, Ill.
Walter Merritt Bartlett ..... Benton Harbor, Mich.
Julian Cox Barton ..... San Antonio, Tex.
James Bernard Berardi ..... Dwight, Ill.
Frank Hartsuff Bethell ..... Ann Arbor, Mich.
Launcelot Minor Blackford ..... Atlanta, Ga.
Theodore Liston Bliss ..... Akron, Ohio
Ralph Bowen ..... Oklahoma City, Okla.
Ernest Lloyd Boylen ..... Portland, Ore.
Russell Stanton Bray ..... Providence, R. I.
Alexander Edward Brown ..... Rochester, Minn.
Charles Stanford Byron ..... Brooklyn, N. Y.

Walter Lawrence Cahall ..... Philadelphia, Pa.
Frank Benjamin Carr ..... Worcester, Mass.
Charles Evans Catchings ..... Woodville, Miss.
John Richard Cavanagh ..... Washington, D. C.
William Edward Chamberlain ..... Philadelphia, Pa.
Charles Belson Chapman ..... Welch, W. Va.
Anthony Caesar Cipollaro ..... New York, N. Y.
Thomas Sterling Claiborne ..... Atlanta, Ga.
Richard James Clark ..... Winchester, Mass.
Milton Bronner Cohen ..... Cleveland, Ohio
Everett Naughtin Collins ..... Cleveland, Ohio
William Johnston Cranston ..... Augusta, Ga.
Burrill B. Crohn ..... New York, N. Y.

Marion Tabb Davidson ..... Birmingham, Ala.
John Staige Davis, Jr. ..... New York, N. Y.
Elbert DeCoursey ..... M. C., U. S. Army
Morris Deitchman ..... Youngstown, Ohio
Samuel Dessoff ..... Washington, D. C.
Bruce Hutchinson Douglas ..... Detroit, Mich.
Ardrey Whidden Downs ..... Edmonton, Alta., Canada
Paul A. Draper ..... Colorado Springs, Colo.
Earl Danford DuBois ..... Portland, Ore.
Garfield George Duncan ..... Philadelphia, Pa.
Harry Anthony Durkin ..... Peoria, Ill.

Herbert Robert Edwards ..... New York, N. Y.
Arthur Carlton Ernstene ..... Cleveland, Ohio
Earl Bradley Erskine ..... Jamaica, L. I., N. Y.
Stanley Erwin ..... Jacksonville, Fla.
Vernon Lawrence Evans ..... Aurora, Ill.
Harold Korb Eynon ..... Collingswood, N. J.

Marcos Fernan-Nunez ..... Milwaukee, Wis.
Maxwell Finland ..... Boston, Mass.
George Fordham ..... Powellton, W. Va.
James Hedges Forsee ..... M. C., U. S. Army
Daniel Parsons Foster ..... Detroit, Mich.
Stuart Oliver Foster ..... Washington, D. C.
George Charles Henry Franklin ..... M. C., U. S. Army
Leslie Howson French ..... Washington, D. C.

Max L. Garon ..... Louisville, Ky.
Warren Monroe Gilbert ..... Rome, Ga.
Edgar Gilmore Givhan, Jr. ..... Birmingham, Ala.
Stanley Milton Goldhamer ..... Ann Arbor, Mich.
Rufus Quitman Goodwin ..... Oklahoma City, Okla.
Roderick John Gordon ..... London, Ont., Canada
James John Gorman ..... El Paso, Tex.
Raymond Leslie Gregory ..... Washington, D. C.
William Hugh Griffith ..... Huron, S. D.
John Carl Grill ..... Milwaukee, Wis.

Ernest Elvin Hadley ..... Washington, D. C.
James Addison Halsted ..... Dedham, Mass.
Jesse Dewey Hamer ..... Phoenix, Ariz.
Leland Potts Hawkins ..... Los Angeles, Calif.
John N. Hayes ..... Saranac Lake, N. Y.
John Herbert Leyda Heintzelman ..... Pittsburgh, Pa.
Louis Max Hickernell ..... Syracuse, N. Y.
Charles Spencer Higley ..... Cleveland, Ohio
John Palmer Hilton ..... Denver, Colo.
Blair Holcomb ..... Portland, Ore.
Frederick Redding Hood ..... Oklahoma City, Okla.
Frank Stephen Horvath ..... Washington, D. C.
Joseph Warren Hundley, Jr. ..... Philadelphia, Pa.
Raymond Hussey ..... Baltimore, Md.

Charles Louis Ianne ..... San Jose, Calif.

Mendel Jacobi ..... Brooklyn, N. Y.
Roy R. Jamieson ..... Chicago, Ill.

Hartwell Joiner ..... Gainesville, Ga.
Oswald Roberts Jones ..... New York, N. Y.

John Leonard Kantor ..... New York, N. Y.
Egon Emil Kattwinkel ..... Auburndale, Mass.
Harold R. Keeler ..... Philadelphia, Pa.
Wilbur Floyd Keller ..... Oklahoma City, Okla.
Edwin John Kepler ..... Rochester, Minn.
Stockton Kimball ..... Buffalo, N. Y.
Edward Sandling King ..... Wake Forest, N. C.
Theodore G. Klumpp ..... Washington, D. C.
Enrique Koppisch ..... San Juan, P. R.
Albert Franklin Kuhl ..... Dayton, Ohio

Louis Harold Landay ..... Pittsburgh, Pa.
Isidore Lattman ..... Washington, D. C.
Fay Atkinson LeFevre ..... Cleveland, Ohio
Noble Day Leonard ..... North Chicago, Ill.
Aleksei A. Leonidoff ..... Poughkeepsie, N. Y.
Robert Milton Lintz ..... New York, N. Y.
Louis Maxwell Lockie ..... Buffalo, N. Y.
Harold Charles Lueth ..... Evanston, Ill.
Jeremiah Fletcher Lutz ..... York, Pa.

Merl Lonner Margason ..... Portland, Ore.
Arthur Ashley Marlow ..... La Jolla, Calif.
Paul Bernard Mason ..... Sheboygan, Wis.
Lorenzo Dow Massey ..... Osceola, Ark.
Joseph Daniel McCarthy ..... Omaha, Nebr.
Clarke M. McColl ..... Detroit, Mich.
Robert Hall McConnell ..... New York, N. Y.
Ernest Perry McCullagh ..... Cleveland, Ohio
Robert Hugh McDonald ..... Cleveland, Ohio
Thomas Hodge McGavack ..... New York, N. Y.
Bernard Edward McGovern ..... San Fernando, Calif.
Ross T. McIntire ..... M. C., U. S. Navy
John Wendell McKenzie ..... Charlottetown, P. E. I., Canada
John McDowell McKinney ..... New York, N. Y.
James Bowron McLester ..... Birmingham, Ala.
Hector James McNeile ..... New York, N. Y.
Edgar Marion McPeak ..... San Antonio, Tex.
Perry Julius Melnick ..... Chicago, Ill.
Harold Russell Merwarth ..... Brooklyn, N. Y.
Solomon George Meyers ..... Detroit, Mich.
William Grady Mitchell ..... San Angelo, Tex.
Herman John Moersch ..... Rochester, Minn.
Merle Wayland Moore ..... Portland, Ore.
Carlyle Morris ..... Metuchen, N. J.
Carlisle Morse ..... Louisville, Ky.
Charles Scott Mudgett ..... M. C., U. S. Army
Bert Ernest Mulvey ..... Oklahoma City, Okla.
Harold A. Murray ..... Newark, N. J.
Elmer Ray Musick ..... Oklahoma City, Okla.

John Ernest Nelson ..... Seattle, Wash.
Charles Fay Nichols ..... Philadelphia, Pa.

Howard Miller Odel ..... Rochester, Minn.
Forrest Ralph Ostrander ..... M. C., U. S. Army

Wendell Heath Paige ..... Brownwood, Tex.
Harold Dwight Palmer ..... Rockford, Ill.
Paul H. Parker ..... Jenkintown, Pa.
Emmet Forrest Pearson ..... Springfield, Ill.
Louis Leo Perkel ..... Jersey City, N. J.
Richard Oscar Pfaff ..... Des Moines, Iowa
Theodore John Pfeffer ..... Racine, Wis.
Charles Aden Poindexter ..... New York, N. Y.
Ralph Emmett Porter ..... U. S. Public Health Service
William Henry Potts, Jr. ..... Dallas, Tex.

Milton James Quinn ..... Winchester, Mass.

William Orville Ramey ..... Cincinnati, Ohio
Edward Randall, Jr. ..... Galveston, Tex.
Stanley Philip Reimann ..... Philadelphia, Pa.
Anthony Joseph Rejent ..... Toledo, Ohio
Clarence E. Reyner ..... Detroit, Mich.
Henry Barber Richardson ..... New York, N. Y.
Hugo Roesler ..... Philadelphia, Pa.
Saul Rosenzweig ..... Detroit, Mich.
William Ward Rucks, Jr. ..... Oklahoma City, Okla.

Zachary Sagal ..... New York, N. Y.
Raymond Arthur Sands ..... Santa Monica, Calif.
David Jacob Sandweiss ..... Detroit, Mich.
Howard Russell Sauder ..... Wheeling, W. Va.
Theresa Scanlan ..... New York, N. Y.
Philipp J. R. Schmahl ..... New York, N. Y.
Henry Lenzen Schmitz ..... Chicago, Ill.
Robert Jacob Schneck ..... Detroit, Mich.
Seymour Crandall Schwartz ..... M. C., U. S. Army
Walter de Mouilpied Scriver ..... Montreal, Que., Canada
William Corr Service ..... Colorado Springs, Colo.
Samuel Charlton Shepard ..... Tulsa, Okla.
Charles Shookoff ..... Brooklyn, N. Y.
Stanley D. Simon ..... Cincinnati, Ohio
Edwin J. Simons ..... Swanville, Minn.
Carter Smith ..... Atlanta, Ga.
Richard Mays Smith ..... Dallas, Tex.
Leon Judah Solway ..... Toronto, Ont., Canada
Louis Sommer ..... Cincinnati, Ohio
Hyman I. Spector ..... St. Louis, Mo.
Frederick George Speidel ..... Louisville, Ky.
Harold Edmond Speight ..... Middletown, Conn.
William Arnold Stafne ..... Moorhead, Minn.
Dean Field Stanley ..... Decatur, Ill.
Robert Morgan Stecher ..... Cleveland, Ohio
Walter Ralph Steiner ..... Hartford, Conn.
Bernard Sternberg ..... Brooklyn, N. Y.
Harold Wentworth Stevens ..... Duxbury, Mass.
Colin Campbell Stewart ..... Hanover, N. H.
Harold Julian Stewart ..... New York, N. Y.
Robert Thomas Sutherland ..... Oakland, Calif.

Earl Richard Templeton ..... Washington, D. C.
Charles Roberts Thomas ..... Chattanooga, Tenn.
Daniel Rees Thomas ..... Knoxville, Tenn.
Cornelius Horace Traeger ..... New York, N. Y.
John William Trask ..... Chelsea, Mass.
John Poag Tucker ..... Cleveland, Ohio

Herbert John Ulrich ..... Buffalo, N. Y.
Harry Eduarde Ungerleider ..... New York, N. Y.

Louis Ashley Van Kleeck ..... Manhasset, N. Y.

Joe Edmund Walker ..... Long Beach, Calif.
Fonso Butler Watkins ..... Morganton, N. C.
Ralph Martin Watkins ..... Cleveland, Ohio
Robert Briggs Watson ..... Wilson Dam, Ala.
Morris M. Weiss ..... Louisville, Ky.
John Murray Welch ..... M. C., U. S. Army
George Louis Weller, Jr. ..... Washington, D. C.
Jacob Werne ..... Jamaica, L. I., N. Y.
Henry L. C. Weyler ..... Providence, R. I.
Joseph Francis Whinery ..... Newark, N. J.
Joseph Hall Whiteley ..... M. C., U. S. Army
Jerome Andrew Whitney ..... Longmeadow, Mass.
James Newton Williams ..... Richmond, Va.
Julius Lane Wilson ..... New Orleans, La.
Frank McLeod Wiseley ..... Findlay, Ohio
Mast Wolfson ..... Monterey, Calif.
Charles Hamilton Wolohon ..... Takoma Park, Washington, D. C.
John Olen Woods ..... New Castle, Pa.
S. Bernard Wortis ..... New York, N. Y.
Arthur Thomas Wyatt ..... Lillington, N. C.

Dwight Moody Young ..... M. C., U. S. Army

Francis Eugene Zemp ..... Columbia, S. C.

At a meeting of the Board of Regents on March 26, the following were elected to Associateship, making a total of 204 new Associates since the preceding Annual Session:

William Arnold Douglas Anderson ..... Memphis, Tenn.

Arthur Carl Bachus ..... Powers, Mich.
Walter Hilmar Baer ..... Peoria, Ill.
Gordon Wesley Balyeat ..... Ann Arbor, Mich.
Andrew L. Banyai ..... Wauwatosa, Wis.
William H. Barker ..... Baltimore, Md.
Maurice C. Barnes ..... Waco, Tex.
Clifford Albert Best ..... M. C., U. S. Army
Henry Grady Bevil ..... Beaumont, Tex.
Edward Bigg ..... Ann Arbor, Mich.
Samuel Blinder ..... New York, N. Y.
Rankin Clay Blount ..... Lexington, Ky.
Joseph Emile Blum, Jr. ..... New Orleans, La.
Charles Andrew Bohnengel ..... New York, N. Y.
Edmund Clyde Boots ..... Pittsburgh, Pa.

DeVere Robert Boyd ..... Muskegon, Mich.
George Nelson Burger ..... Athens, Ohio
George Warren Burnett ..... Oil City, Pa.

Joseph Bishop Cady ..... Rochester, Minn.
Franklin Chester Cassidy ..... Livermore, Calif.
Edwin Gurney Clark ..... Nashville, Tenn.
James W. Colella ..... Binghamton, N. Y.
Jay Cecil Crager ..... Beaumont, Tex.
Lloyd Lorenzo Cullimore ..... Provo, Utah
Haydn Harrison Cutler ..... Rochester, Minn.

Joseph Steven D'Antoni ..... New Orleans, La.
Boni James De Laureal ..... New Orleans, La.
Nelson Wright Diebel ..... Detroit, Mich.
Ray S. Dixon ..... Detroit, Mich.
Ralph Lafayette Drake ..... Wichita, Kan.

Paul Strimple Fancher ..... M. C., U. S. Army
Robert Hanna Felix ..... Lexington, Ky.
David Ferguson, Jr. ..... Washington, D. C.
Hugh Francis Folsom ..... Southborough, Mass.
Hugh Frederick Freidell ..... Santa Barbara, Calif.
Chester Sebastian Fresh ..... New Orleans, La.
Linus Jos. Foster ..... Detroit, Mich.
Silas Crume Fulmer ..... Little Rock, Ark.

Lawrence Bernard Gang ..... Huntington, W. Va.
Jay McKinley Garner ..... Winnetka, Ill.
Thomas Cresson Garrett ..... Philadelphia, Pa.
Frederick A. J. Geier ..... Washington, D. C.
Olin Burr Gober ..... Temple, Tex.
Frederick Goldman ..... Galveston, Tex.
Kenneth George Gould ..... M. C., U. S. Army
John Quentin Griffith ..... Philadelphia, Pa.
Randolph Bryan Grinnan, Jr. ..... Norfolk, Va.
Edward Bertram Grossman ..... New York, N. Y.
James Roby Gudger ..... New York, N. Y.

James Lonnie Hamilton ..... Chattanooga, Tenn.
Paul Victor Hamilton ..... Cincinnati, Ohio
Maurice Hardgrove ..... Milwaukee, Wis.
Leon Hughes Hetherington ..... Pittsburgh, Pa.
Clifton Keck Himmelsbach ..... Lexington, Ky.
Milford Leroy Hobbs ..... Burlington, Vt.
Emory Dallas Hollar ..... Vernon, Tex.
J. Sudler Hood ..... Clearwater, Fla.
William James Hutchinson ..... Galveston, Tex.

William Reginald Jackson ..... Kansas City, Mo.
Joseph Francis Jenovese ..... Rochester, Minn.
Carl Edward Johnson ..... Morgantown, W. Va.
Edward Morgan Jones ..... Endicott, N. Y.
Robert Harold Jones ..... Montgomery, W. Va.

Aaron Arnold Karan ..... Liberty, N. Y.
Franklin Hartman Kilgore ..... Houston, Tex.
Otis Gardner King ..... Bluefield, W. Va.

Alfred Edward Koehler ..... Santa Barbara, Calif.
Charles John Koerth ..... San Antonio, Tex.
Joseph Rudolph Kriz ..... New Orleans, La.

Joseph Durel Landry ..... New Orleans, La.
Charles Wesley Layne ..... Newburgh, N. Y.
Albert Theodore Leatherbarrow ..... Hampton Station, N. B., Can.
Seaborn Joseph Lewis ..... Beaumont, Tex.
Julian Sax Long ..... Wilkes-Barre, Pa.
Philip Lukens ..... Ambler, Pa.

Tim Joseph Manson ..... Chattanooga, Tenn.
Frederick Eugene Marsh ..... Chattanooga, Tenn.
Floyd Thomas McIntire ..... San Angelo, Tex.
Delbert H. McNamara ..... Santa Barbara, Calif.
James Douglas Laurance McPheeters ..... Chattanooga, Tenn.
John Patrick McVay ..... Seattle, Wash.
Francis Ralph Meyers ..... Paterson, N. J.
R. Bretney Miller ..... Boston, Mass.
Samuel Mirsky ..... Ottawa, Ont., Can.
Lester M. Morrison ..... Philadelphia, Pa.
Emma Sadler Moss ..... New Orleans, La.

Walter Scott Neff ..... Virginia, Minn.
Virgil Frank Neumann ..... Norwich, Conn.
Thomas Ochsner Nuzum ..... Janesville, Wis.

Arthur Burke O'Brien ..... Rochester, N. Y.
Louis Bonner Owens ..... Cincinnati, Ohio

Robert Clinton Page ..... Mount Vernon, N. Y.
Sol Parent ..... Newark, N. J.
Aaron Robert Peskin ..... New York, N. Y.
Helen Sinclair Pittman ..... Boston, Mass.
Francis Marion Pottenger, Jr. ..... Monrovia, Calif.
Harry William Primakoff ..... Baltimore, Md.

Harry Malcolm Read ..... York, Pa.
Edward Conrad Reifenstein, Jr. ..... Syracuse, N. Y.
Murray Lambert Rich ..... Covington, Ky.
Archie Marvin Roberts ..... Los Angeles, Calif.
Frank Hurd Robinson, Jr. ..... New York, N. Y.
John Roy Rodger ..... Bellaire, Mich.
Abraham Rudy ..... Boston, Mass.
Nelson Gorham Russell, Jr. ..... Buffalo, N. Y.

Otis B. Schreuder ..... M. C., U. S. Army
Grady Oscar Segrest ..... Mobile, Ala.
Joseph Haskell Shaffer ..... Detroit, Mich.
William W. Shapiro ..... Chicago, Ill.
John Charles Sharpe ..... Omaha, Nebr.
Walter Charles Smallwood ..... Long Beach, Calif.
Opie Norris Smith ..... Greensboro, N. C.
Martin Jos. Sokoloff ..... Philadelphia, Pa.
Harold Jones Starr ..... Chattanooga, Tenn.
Alfred Stengel, Jr. ..... Philadelphia, Pa.
Ralph Eugene Swope ..... New York, N. Y.
Richard Carmichael Tilghman ..... Baltimore, Md.

Harry Burger Thomas ..... York, Pa.
Harry Edward Thompson ..... Tucson, Ariz.
Lucius Newton Todd ..... Augusta, Ga.
Arthur Raymond Twiss ..... Ann Arbor, Mich.

Hiram Eugene Upton ..... Burlington, Vt.

Don Conklin Wakeman ..... Topeka, Kan.
Frank Bolles Wakeman ..... M. C., U. S. Army
Walter Weissenborn ..... Hartford, Conn.
John Francis Whalen ..... Altadena, Calif.
Merritt Bryant Whitten ..... Dallas, Tex.
Walter John Wilson, Jr. ..... Detroit, Mich.
Francis Roman Wise ..... York, Pa.
Sidney Elmer Wolpaw ..... Cleveland, Ohio

Charles Tindal Young ..... M. C., U. S. Army

New Life Members

The following Fellows have become Life Members of the American College of Physicians on March 9 and March 15, respectively:

Dr. Frank Bethel Cross, Brooklyn, N. Y.
Dr. James Alexander Lyon, Washington, D. C.

Gifts to the College Library

Grateful acknowledgment is made of the receipt of the following gifts to the College Library of publications by members:

Reprints

Dr. Archie H. Beard, F.A.C.P., Minneapolis, Minn.—5 reprints;
Dr. Warren Coleman, F.A.C.P., Augusta, Ga.—2 reprints;
Dr. Frank J. Holroyd (Associate), Princeton, W. Va.—1 reprint;
Dr. Louis I. Kramer, F.A.C.P., Providence, R. I.—2 reprints;
Dr. Fay A. LeFevre, F.A.C.P., Cleveland, Ohio—2 reprints;
Dr. Oliver T. Osborne, F.A.C.P., New Haven, Conn.—1 reprint;
Dr. Samuel S. Paley (Associate) New York, N. Y.—1 reprint;
Dr. Kenneth Phillips, F.A.C.P., Miami, Fla.—2 reprints;
Dr. Jacob Schwartz (Associate), Brooklyn, N. Y.—1 reprint;
Dr. Albert Soiland, F.A.C.P., Los Angeles, Calif.—5 reprints;
Dr. Peter J. Steincrohn (Associate), Hartford, Conn.—1 reprint.

Virginia Sectional Meeting

Fellows and Associates of the American College of Physicians from the State of Virginia held a meeting during March in Norfolk, with forty members present. The Virginia group is now holding three meetings a year, and each one is becoming more attractive and of more benefit. One is a social meeting and the other two are strictly scientific. The meetings are held in different parts of the State. Dr. T. Dewey Davis, F.A.C.P., of Richmond is chairman of the Virginia section, and Dr. Charles M. Caravati, F.A.C.P., of Richmond is the secretary. The group and the officers function under Dr. J. Morrison Hutcheson, F.A.C.P., who has been the Governor for the State of Virginia for several years.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., addressed a joint meeting of the Section on Research, Academy of Stomatology, Section on Research, Philadelphia County Dental Society and Section on Stomatology, Philadelphia County Medical Society, on Friday, February 24, 1939, on "The Rôle of Deficiency Disease in Dentistry, with Special Reference to Vitamins and Minerals."

Dr. Isidore W. Held, F.A.C.P., Clinical Professor of Medicine at New York University College of Medicine, addressed the 93rd annual banquet of the Northern Medical Association of Philadelphia, March 20, on "Jefferson, My Alma Mater; and Philadelphia as a Medical Center." Dr. David Riesman, F.A.C.P., Philadelphia, acted as toastmaster, and Dr. E. J. G. Beardsley, F.A.C.P., Clinical Professor of Medicine at Jefferson Medical College, was another of the speakers.

Dr. Hubert C. King, F.A.C.P., President of the Academy of Medicine of Cleveland delivered an address on "The Physician," in connection with a forum discussion on the social and economic aspects of medicine, sponsored by Western Reserve University School of Medicine from March 17 to May 9. Dr. King's address was delivered on March 31, and dealt with the recent trends in premedical and medical education, certification in specialties, the distribution of physicians in the United States, physicians' incomes as revealed in special surveys, etc. His paper was intended to reveal the rôle of the physician in connection with the forum on "The Physician and Dentist."

Dr. J. C. Doane, Professor of Clinical Medicine of Temple University Medical School of Philadelphia addressed the York County Medical Society at York, Pa., on Saturday, March 18, 1939. The subject was "Alcoholism, Its Diagnosis and Treatment"; also the Chester County Medical Society at West Chester, Pa., on Tuesday, March 21, 1939. The subject was "Clinical Interpretation of the Symptoms Pain."

RECENT ANNOUNCEMENTS

American Board of Internal Medicine, Inc.

Written examinations for certification by the American Board of Internal Medicine will be held in various sections of the United States on the third Monday in October and the third Monday in February.

Formal application must be received by the Secretary before August 20, 1939 for the October 16, 1939 examination, and on or before January 1 for the February 19, 1940 examination.

Application forms may be obtained from Dr. William S. Middleton, Secretary-Treasurer, 1301 University Avenue, Madison, Wisconsin, U. S. A.

The Fourteenth Scientific Sessions of the American Heart Association will be held at the Hotel Jefferson, St. Louis, Missouri. The general cardiac program will be given on Friday, May 12, and the program of the Section for the Study of the Peripheral Circulation on Saturday, May 13.

The 24th Annual meeting of the American Association of Industrial Physicians and Surgeons with the American Conference on Occupational Diseases and Industrial Hygiene will be held at the Hotel Statler, Cleveland, Ohio, June 5, 6, 7, and 8, 1939. A program of timely interest and importance will be presented by speakers of outstanding experience in all of the medical and engineering problems involved in industrial health. A cordial invitation is extended to all whose interests bring them in contact with these problems. Information regarding hotel accommodations, etc., may be obtained from A. G. PARK, Convention Manager, 540 North Michigan Avenue, Chicago.

The American Physicians' Art Association, composed of members in the United States, Canada, and Hawaii, will hold its second Art Exhibit in the City Art Museum of St. Louis, May 14–20, 1939, during the annual session of the American Medical Association. Art pieces will be accepted for this art show in the following classifications: (1) oils both (*a*) portrait and (*b*) landscape; (2) water colors; (3) sculpture; (4) photographic art; (5) etchings; (6) ceramics; (7) pastels; (8) charcoal drawings; (9) book-binding; (10) wood carving; (11) metal work (jewelry). Practically all pieces sent in will be accepted. There will be over 60 valuable prize awards. For details of membership in this Association and rules of the Exhibit, kindly write to Max Thorek, M.D., Secretary, 850 Irving Park Blvd., Chicago, Ill., or F. H. Redewill, M.D., President, 521–536 Flood Bldg., San Francisco, Calif.

The 63d annual convention of the American Association on Mental Defect will be held at the Palmer House in Chicago, Illinois, from May 3d to 6th, inclusive.

The Balkan Medical Union, in session at Istanbul, for the 5th Medical Week,

having taken into consideration the terrible sufferings which a total war will bring upon the civil population of open towns together with the total lack of any adequate means of protection,

and having discovered that even in its restricted form the project of "sanitary towns" has not yet been adopted, and that all efforts made to protect civilians against chemical warfare have until now remained as proposals only, and that even the protocol prohibiting the use of asphyxiating gas has not yet been ratified by all nations,

has therefore decided to address itself to doctors of every nation with an appeal to take active measures and to fulfill this professional and humanitarian duty of awakening and stirring public opinion.

The Balkan Medical Union believes that only enlightened international opinion can make plain the imminence of the danger and the proved uselessness, even for the victor, of these terrible atrocities, and can thus lead to effective action.

The immutable truth that

hate breeds only hate, and atrocity breeds vengeance must be impressed on everyone.

PROF. DR. BENSIS, DR. SCARAMANGA (Athènes), DR. ZIKA MARKOVIÇ, PROF. DR. K. SAHOVIÇ, DR. M. SIMOVIÇ (Beograd), PROF. DR. GHEORGHIU, DR. POPESCU BUZEU (Bucarest), PROF. DR. ÂKIL MUHTAR ÖZDEN, PROF. SEDAT TAVAT, PROF. DR. A. SÜHEYL UNVER (İstanbul).

OBITUARIES

DR. DONALD GREGG

Dr. Donald Gregg (Fellow and Life Member), of Wellesley, died January 6, 1939 at Phillips House, Massachusetts General Hospital. He was in his sixtieth year.

Born in Hartford, Connecticut, he moved as a child to Colorado Springs, Colorado, attending the public schools there. He prepared for college at Cutler Academy, graduated from Harvard College in 1902 and received his degree from Harvard Medical School in 1907. He served his internship during 1908–1909 at the Massachusetts General Hospital, after which he served four years as resident physician of the Philippine General Hospital at Manila, Philippine Islands. During one year there he was assistant professor of tropical medicine at the University of the Philippines.

Dr. Gregg returned to the United States in 1912 and began practicing in Wellesley. He became associated with Dr. Channing in the direction of the Channing Sanitarium at Wellesley, taking full charge at the time of Dr. Channing's death in 1922.

Among his affiliations were memberships in the American Medical Association, Massachusetts Medical Society, American College of Physicians, American Neurological Association, American Psychiatric Association, New England Society of Psychiatry, Association for Research in Nervous and Mental Disease and American Psychopathological Association.

His widow, three brothers and three sisters survive him.

WILLIAM B. BREED, M.D., F.A.C.P.,
Governor for Massachusetts.

DR. JAMES WALLACE ESLER

James Wallace Esler, of *2737* Devonshire Place, N.W., Washington, D. C., died December 15, 1938, of sarcoma of the intestines. He was only forty-four years old and had been elected to Associateship in the American College of Physicians two years before his death. A prominent cardiologist in the national capital, he had a promising career tragically shortened. Very well liked by everyone, he has already been greatly missed.

Dr. Esler was born in Tarentum, Pa., October *27*, 1894. He received an A.B degree in 1916 from Washington and Jefferson College, and in 1920, an M.D. degree from the University of Pennsylvania School of Medicine. He spent the next year as an Instructor in Physiology and as a postgraduate research worker in physiology at his medical Alma Mater. After interning in the Pennsylvania Hospital, Philadelphia, from 1921 to 1923, he served for one year as chief resident at St. Christopher's Hospital, Philadelphia. From 1927 to 1928 he did postgraduate study in cardiology at the Massachusetts General Hospital, Boston.

From the time he began the practice of cardiology in the District of Columbia in 1928 he held the Professorship of Clinical Cardiology at the Georgetown University School of Medicine and served as an Associate in Medicine and Chief of the Cardiac clinics at Georgetown University Hospital. He also became associated later with the Central Dispensary and Emergency Hospital, and Garfield Memorial Hospital. Dr. Esler was a member of the American Medical Association, the Medical Society of the District of Columbia, and the Washington Heart Association, of which he was secretary for years and later president. He was a former member of the Allegheny County Medical Society (Pittsburgh).

Surviving are his widow, Mrs. Lillian Esler, a son, James Wallace Esler, Jr., and a brother, Russel J. Esler.

WALLACE M. YATER, M.D., F.A.C.P.,
Governor for the District of Columbia.

DR. LESSER KAUFFMAN

Dr. Lesser Kauffman, a Fellow of the American College of Physicians since 1916, died in Buffalo, New York, March 11, 1939, from a "heart attack."

Dr. Kauffman was born in Germany April 8, 1876, came to America when he was quite young and settled in Rochester, New York. He completed his undergraduate studies at the University of Rochester and was graduated from the University of Buffalo in 1904. He soon became associated with Dr. James W. Putnam, then Professor of Neurology at the University of Buffalo. Dr. Kauffman continued the practice of neurology and psychiatry throughout his medical career.

Dr. Kauffman was very active in the General Alumni Association of the University of Buffalo, and was first President of that group. His principal outside interest was music. He was most active in the Symphony Society and his work in bringing to Buffalo music of the highest type contributed to the greater appreciation of music in the city and the support of fine music throughout the country. He was also active in the Museum of Science and the Buffalo Historical Society.

Dr. Kauffman's activities in his profession and as a citizen were of the highest type.

Dr. Kauffman was unmarried and is survived by a sister in Pittsburgh and a brother in Rochester.

NELSON G. RUSSELL, M.D., F.A.C.P.,
Governor for Western New York.